PYRAZOLO '3,4-B! PYRIDINE COMPOUNDS, AND THEIR USE AS PHOSPHODIESTERASE TYPE 4 (PDE4) INHIBITORS

The present invention relates to pyrazolo[3,4-b]pyridine compounds, processes for their preparation, intermediates usable in these processes, and pharmaceutical compositions containing the compounds. The invention also relates to the use of the pyrazolo[3,4-b]pyridine compounds in therapy, for example as inhibitors of phosphodiesterase type IV (PDE4) and/or for the treatment and/or prophylaxis of inflammatory and/or allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis or allergic rhinitis.

Background to the Invention

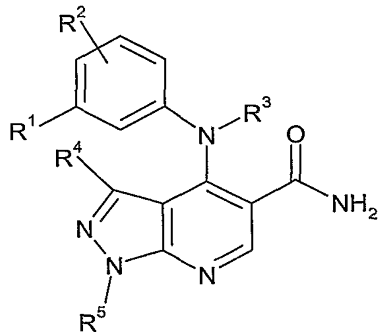
US 3,979,399, US 3,840,546, and US 3,966,746 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxamides wherein the 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 3-6-membered heterocyclic group such as pyrrolidino, piperidino and piperazino. The compounds are disclosed as central nervous system depressants useful as ataractic, analgesic and hypotensive agents.

US 3,925,388, US 3,856,799, US 3,833,594 and US 3,755,340 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxylic acids and esters. The 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 5-6-membered heterocyclic group in which an additional nitrogen is present such as pyrrolidino, piperidino, pyrazolyl, pyrimidinyl, pyridazinyl or piperazinyl. The compounds are mentioned as being central nervous system depressants useful as ataractic agents or tranquilisers, as having antiinflammatory and analgesic properties. The compounds are mentioned as increasing the intracellular concentration of adenosine-3',5'-cyclic monophosphate and for alleviating the symptoms of asthma.

H. Hoehn et al., *J. Heterocycl. Chem.*, 1972, 9(2), 235-253 discloses a series of 1*H*-pyrazolo[3,4-b]pyridine-5-carboxylic acid derivatives with 4-hydroxy, 4-chloro, 4-alkoxy, 4-hydrazino, and 4-amino substituents.

CA 1003419, CH 553 799 and T.Denzel, *Archiv der Pharmazie*, 1974, 307(3), 177-186 disclose 4,5-disubstituted 1*H*-pyrazolo[3,4-b]pyridines unsubstituted at the 1-position.

Japanese laid-open patent application JP-2002-20386-A (Ono Yakuhin Kogyo KK) published on 23 January 2002 discloses pyrazolopyridine compounds of the following formula:



JP-2002-20386-A
(Ono)

wherein R^1 denotes 1) a group $-OR^6$, 2) a group $-SR^7$, 3) a C2-8 alkynyl group, 4) a nitro group, 5) a cyano group, 6) a C1-8 alkyl group substituted by a hydroxy group or a C1-8 alkoxy group, 7) a phenyl group, 8) a group $-C(O)R^8$, 9) a group $-SO_2NR^9R^{10}$, 10) a group $-NR^{11}SO_2R^{12}$, 11) a group $-NR^{13}C(O)R^{14}$ or 12) a group $-CH{=}NR^{15}$. R^6 and R^7 denote i) a hydrogen atom, ii) a C1-8 alkyl group, iii) a C1-8 alkyl group substituted by a C1-8 alkoxy group, iv) a trihalomethyl group, v) a C3-7 cycloalkyl group, vi) a C1-8 alkyl group substituted by a phenyl group or vii) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms. R^2 denotes 1) a hydrogen atom or 2) a C1-8 alkoxy group. R^3 denotes 1) a hydrogen atom or 2) a C1-8 alkyl group. R^4 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group, 5) a phenyl group which may be substituted by 1-3 halogen atoms or 6) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms. R^5 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group or 5) a phenyl group which may be substituted by 1-3 substituents. In group R^3, a hydrogen atom is preferred. In group R^4 , methyl, ethyl, cyclopropyl, cyclobutyl or cyclopentyl are preferred. The compounds of JP-2002-20386-A are stated as having PDE4 inhibitory activity and as being useful in the prevention and/or treatment of inflammatory diseases and many other diseases.

1,3-Dimethyl-4-(arylamino)-pyrazolo[3,4-b]pyridines with a 5-C(O)NH_2 substituent similar or identical to those in JP-2002-20386-A were disclosed as orally active PDE4 inhibitors by authors from Ono Pharmaceutical Co. in: H. Ochiai et al., *Bioorg. Med. Chem. Lett.*, 5th January 2004 issue, vol. 14(1), pp. 29-32 (available on or before 4th December 2003 from the Web version of the journal: "articles in press").

EP 0 076 035 A1 (ICI Americas) discloses pyrazolo[3,4-b]pyridine derivatives as central nervous system depressants useful as tranquilisers or ataractic agents for the relief of anxiety and tension states.

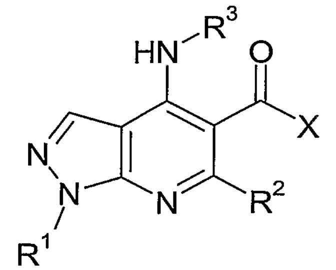
The compound cartazolate, ethyl 4-(n-butylamino)-1-ethyl-1H-pyrazolo[3,4-b]-pyridine-5-carboxylate, is known. J.W. Daly et al., *Med. Chem. Res.*, 1994, 4, 293-306 and D. Shi et al., *Drug Development Research*, 1997, 42, 41-56 disclose a series of 4-

(amino)substituted 1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid derivatives, including ethyl 4-cyclopentylamino-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate, and their affinities and antagonist activities at A_1- and A_{2A}-adenosine receptors, and the latter paper discloses their affinities at various binding sites of the $GABA_A$-receptor channel. S. Schenone et al., *Bioorg. Med. Chem. Lett.*, 2001, 11, 2529-2531, and F. Bondavalli et al., *J. Med. Chem.*, 2002, vol. 45 (Issue 22, 24 October 2002, allegedly published on Web 09/24/2002), pp. 4875-4887 disclose a series of 4-amino-1-(2-chloro-2-phenylethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl esters as A_1-adenosine receptor ligands.

WO 02/060900 A2 appears to disclose, as MCP-1 antagonists for treatment of allergic, inflammatory or autoimmune disorders or diseases, a series of bicyclic heterocyclic compounds with a -C(O)-NR^4-C(O)-NR^5R^6 substituent, including isoxazolo[5,4-b]pyridines and 1*H*-pyrazolo[3,4-b]pyridines (named as pyrazolo[5,4-b]pyridines) with the -C(O)-NR^4-C(O)-NR^5R^6 group as the 5-substituent and optionally substituted at the 1-, 3-, 4-, and/or 6-positions. Bicyclic heterocyclic compounds with a –C(O)NH_2 substituent instead of the -C(O)-NR^4-C(O)-NR^5R^6 substituent are alleged to be disclosed in WO 02/060900 as intermediates in the synthesis of the -C(O)-NR^4-C(O)-NR^5R^6 substituted compounds.

WO 00/15222 (Bristol-Myers Squibb) discloses *inter alia* pyrazolo[3,4-b]pyridines having *inter alia* a C(O)-X_1 group at the 5-position and a group E_1 at the 4-position of the ring system. Amongst other things, X_1 can for example be -OR_9, -N(R_9)(R_{10}) or -N(R_5)(-A_2-R_2), and E_1 can for example be -NH-A_1-cycloalkyl, -NH-A_1-substituted cycloalkyl, or -NH-A_1-heterocyclo; wherein A_1 is an alkylene or substituted alkylene bridge of 1 to 10 carbons and A_2 can for example be a direct bond or an alkylene or substituted alkylene bridge of 1 to 10 carbons. The compounds are disclosed as being useful as inhibitors of cGMP phosphodiesterase, especially PDE type V, and in the treatment of various cGMP-associated conditions such as erectile dysfunction. Compounds with a cycloalkyl or heterocyclo group directly attached to -NH- at the 4-position of the pyrazolo[3,4-b]pyridine ring system and/or having PDE4 inhibitory activity do not appear to be disclosed in WO 00/15222.

Copending patent application PCT/EP03/11814, filed on 12 September 2003 in the name of Glaxo Group Limited, and incorporated herein by reference, discloses pyrazolo[3,4-b]pyridine compounds or salts thereof with a 4-NHR^3 group and a 5-C(O)-X group, according to this formula (I):



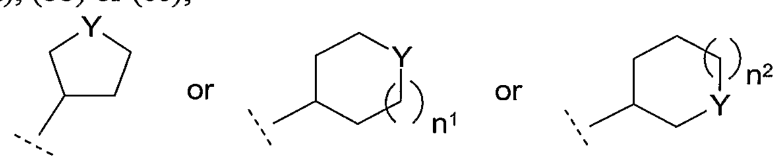
(I)

wherein:

R^1 is C_{1-4}alkyl, C_{1-3}fluoroalkyl, $-CH_2CH_2OH$ or $-CH_2CH_2CO_2C_{1-2}$alkyl;

R^2 is a hydrogen atom (H), methyl or C_1fluoroalkyl;

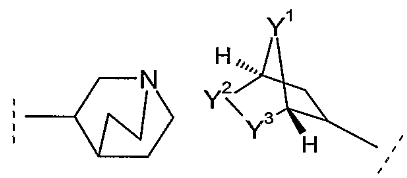
R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc);



(aa) (bb) (cc)

in which n^1 and n^2 independently are 1 or 2; and in which Y is O, S, SO_2, or NR^{10};

or R^3 is a bicyclic group (dd) or (ee):



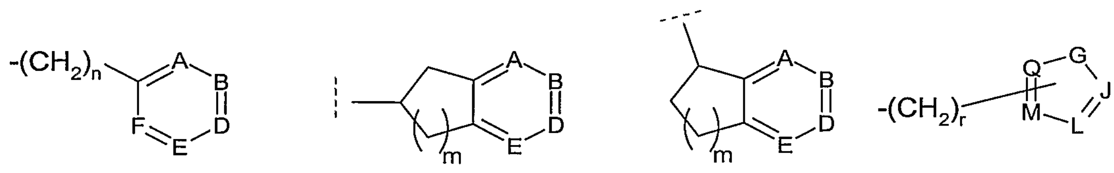
(dd) (ee) ;

and wherein X is NR^4R^5 or OR^{5a}.

In PCT/EP03/11814, R^4 is a hydrogen atom (H); C_{1-6}alkyl; C_{1-3}fluoroalkyl; or C_{2-6}alkyl substituted by one substituent R^{11}.

In PCT/EP03/11814, R^5 can be: a hydrogen atom (H); C_{1-8}alkyl; C_{1-8} fluoroalkyl; C_{3-8}cycloalkyl optionally substituted by a C_{1-2}alkyl group; $-(CH_2)_n{}^4-C_{3-8}$cycloalkyl optionally substituted, in the $-(CH_2)_n{}^4-$ moiety or in the C_{3-8}cycloalkyl moiety, by a C_{1-2}alkyl group, wherein n^4 is 1, 2 or 3; C_{2-6}alkyl substituted by one or two independent substituents R^{11}; $-(CH_2)_n{}^{11}-C(O)R^{16}$; $-(CH_2)_n{}^{12}-C(O)NR^{12}R^{13}$; $-CHR^{19}-C(O)NR^{12}R^{13}$; $-(CH_2)_n{}^{12}-C(O)OR^{16}$; $-(CH_2)_n{}^{12}-C(O)OH$; $-CHR^{19}-C(O)OR^{16}$; $-CHR^{19}-C(O)OH$; $-(CH_2)_n{}^{12}-SO_2-NR^{12}R^{13}$; $-(CH_2)_n{}^{12}-SO_2R^{16}$; or $-(CH_2)_n{}^{12}-CN$; $-(CH_2)_n{}^{13}$-Het; or optionally substituted phenyl.

Alternatively, in PCT/EP03/11814, R^5 can have the sub-formula (x), (y), (y1) or (z):



(x) (y) (y1) (z)

wherein in sub-formula (x), n = 0, 1 or 2; in sub-formula (y) and (y1), m = 1 or 2; and in sub-formula (z), r = 0, 1 or 2; and wherein in sub-formula (x) and (y) and (y1), none, one or two of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^+-O^-) provided that no more than one of A, B, D, E and F is nitrogen-oxide, and the remaining of A, B, D, E and F are independently CH or CR^6; and provided that when n is 0 in sub-formula (x) then one or two of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^+-O^-) and no more than one of A, B, D, E and F is nitrogen-oxide;

In PCT/EP03/11814, each R^6, independently of any other R^6 present, is: a halogen atom; C_{1-6}alkyl; C_{1-4}fluoroalkyl; C_{1-4}alkoxy; C_{1-2}fluoroalkoxy; C_{3-6}cycloalkyloxy; -C(O)R^{16a}; -C(O)OR^{30}; -S(O)$_2$-R^{16a}; R^{16a}-S(O)$_2$-NR^{15a}-; R^7R^8N-S(O)$_2$-; C_{1-2}alkyl-C(O)-R^{15a}N-S(O)$_2$-; C_{1-4}alkyl-S(O)-; Ph-S(O)-; R^7R^8N-CO-; -NR^{15}-C(O)R^{16}; R^7R^8N; OH; C_{1-4}alkoxymethyl; C_{1-4}alkoxyethyl; C_{1-2}alkyl-S(O)$_2$-CH_2-; R^7R^8N-S(O)$_2$-CH_2-; C_{1-2}alkyl-S(O)$_2$-NR^{15a}-CH_2-; -CH_2-OH; -CH_2CH_2-OH; -CH_2-NR^7R^8; -CH_2-CH_2-NR^7R^8; -CH_2-C(O)OR^{30}; -CH_2-C(O)-NR^7R^8; -CH_2-NR^{15a}-C(O)-C_{1-3}alkyl; -$(CH_2)_{n^{14}}$-Het^1 where n^{14} is 0 or 1; cyano (CN); Ar^{5b}; or phenyl, pyridinyl or pyrimidinyl wherein the phenyl, pyridinyl or pyrimidinyl independently are optionally substituted by one or two of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

or two adjacent R^6 taken together can be –O–(CMe_2)–O– or –O–$(CH_2)_{n^{14}}$–O– where n^{14} is 1 or 2.

In PCT/EP03/11814, in sub-formula (z), G is O or S or NR^9 wherein R^9 is a hydrogen atom (H), C_{1-4}alkyl or C_{1-4}fluoroalkyl; none, one, two or three of J, L, M and Q are nitrogen; and the remaining of J, L, M and Q are independently CH or CR^6 where R^6, independently of any other R^6 present, is as defined therein.

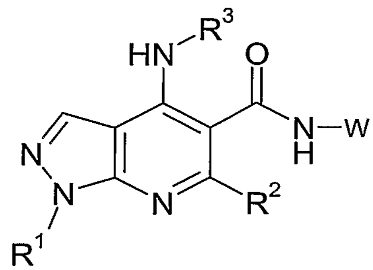
The pyrazolo[3,4-b]pyridine compounds of formula (I) and salts thereof disclosed in PCT/EP03/11814 are disclosed as being inhibitors of phosphodiesterase type IV (PDE4), and as being useful for the treatment and/or prophylaxis of an inflammatory and/or

allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis, or allergic rhinitis.

The Invention

We have now found new pyrazolo[3,4-b]pyridine compounds, having a -C(O)-NH-W substituent at the 5-position of the pyrazolo[3,4-b]pyridine ring system, which compounds inhibit phosphodiesterase type IV (PDE4).

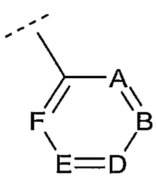
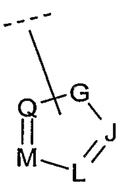
The present invention therefore provides a compound of formula (I) or a salt thereof (in particular, a pharmaceutically acceptable salt thereof):



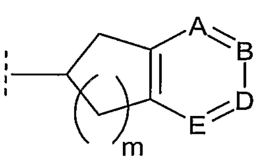
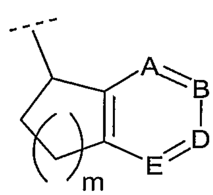
(I)

wherein:

W is Ar, $-CR^4R^5Ar$ or a group (y) or (y1) wherein:

Ar =  or  ,

(x) (z)

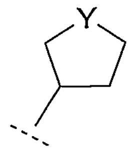
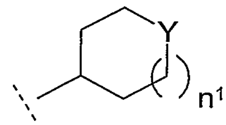
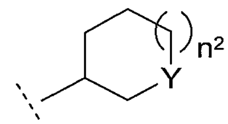
(y) =  and (y1) = 

wherein m = 1 or 2

R^1 is C_{1-4}alkyl, C_{1-3}fluoroalkyl, or $-CH_2CH_2OH$;

R^2 is C_{2-6}alkyl, C_{3-6}cycloalkyl or $-(CH_2)n^4C_{3-6}$cycloalkyl, wherein n^4 is 1 or 2;

R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc);

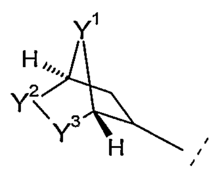
 or  or 

(aa) (bb) (cc)

in which n^1 and n^2 independently are 1 or 2; and in which Y is O, S, SO_2, or NR^{10}; where R^{10} is a hydrogen atom (H), C_{1-2}alkyl, C_{1-2}fluoroalkyl, $CH_2C(O)NH_2$, $C(O)NH_2$, C(O)NHMe, C(O)-C_{1-2}alkyl, C(O)-C_1fluoroalkyl or -C(O)-CH_2O-C_{1-2}alkyl;

and wherein in R^3 the C_{3-8}cycloalkyl or the heterocyclic group of sub-formula (aa), (bb) or (cc) is optionally substituted on a ring carbon with one or two substituents independently being oxo (=O); OH; C_{1-2}alkoxy; C_{1-2}fluoroalkoxy; NHR^{21} wherein R^{21} is a hydrogen atom (H) or C_{1-4} straight-chain alkyl; C_{1-2}alkyl; C_{1-2}fluoroalkyl; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NHR^{22}$ wherein R^{22} is H or C_{1-2}alkyl; $-C(O)OR^{23}$ wherein R^{23} is H or C_{1-2}alkyl; $-C(O)NHR^{24}$ wherein R^{24} is H or C_{1-2}alkyl; $-C(O)R^{25}$ wherein R^{25} is C_{1-2}alkyl; fluoro; hydroxyimino (=N-OH); or (C_{1-4}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-4}alkyl); and wherein any OH, alkoxy, fluoroalkoxy or NHR^{21} substituent is not substituted at the R^3 ring carbon attached (bonded) to the -NH- group of formula (I) and is not substituted at either R^3 ring carbon bonded to the Y group of the heterocyclic group (aa), (bb) or (cc);

and wherein, when R^3 is optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl, then the cycloalkenyl is optionally substituted with one substituent being fluoro or C_{1-2}alkyl or two substituents independently being fluoro or methyl , and the R^3 ring carbon bonded to the -NH- group of formula (I) does not partake in the cycloalkenyl double bond;



or R^3 is a bicyclic group of sub-formula (ee): (ee) wherein Y^1, Y^2 and Y^3 independently are CH_2 or oxygen (O) provided that no more than one of Y^1, Y^2 and Y^3 is oxygen (O);

and wherein:

R^4 and R^5 are independently a hydrogen atom (H), methyl, ethyl, n-propyl, isopropyl, C_{1-2}fluoroalkyl, cyclopropyl, $-CH_2OR^{4a}$, $-CH(Me)OR^{4a}$, or $-CH_2CH_2OR^{4a}$, wherein R^{4a} is a hydrogen atom (H), methyl (Me), or C_1fluoroalkyl such as CF_3 or CHF_2.

and wherein, in sub-formula (x) (y) and (y1):

A is $C-R^{6A}$, nitrogen (N) or nitrogen-oxide (N^+-O^-),
B is $C-R^{6B}$, nitrogen (N) or nitrogen-oxide (N^+-O^-),
D is $C-R^{6D}$, nitrogen (N) or nitrogen-oxide (N^+-O^-),
E is $C-R^{6E}$, nitrogen (N) or nitrogen-oxide (N^+-O^-),
F is $C-R^{6F}$, nitrogen (N) or nitrogen-oxide (N^+-O^-),

wherein, R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} independently are: a hydrogen atom (H), a halogen atom; C_{1-6}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl); C_{1-4}fluoroalkyl (e.g. C_{1-2}fluoroalkyl); C_{3-6}cycloalkyl; C_{1-4}alkoxy (e.g. C_{1-2}alkoxy); C_{1-2}fluoroalkoxy; C_{3-6}cycloalkyloxy; $-C(O)R^{16a}$; $-C(O)OR^{30}$; $-S(O)_2-R^{16a}$ (e.g. C_{1-2}alkyl-$S(O)_2$-); $R^{16a}-S(O)_2-NR^{15a}$- (e.g. C_{1-2}alkyl-$S(O)_2$-NH-); $R^7R^8N-S(O)_2$-; C_{1-2}alkyl-C(O)-$R^{15a}N-S(O)_2$-; C_{1-4}alkyl-S(O)-, Ph-S(O)-, R^7R^8N-CO-; $-NR^{15}-C(O)R^{16a}$; R^7R^8N; nitro ($-NO_2$); OH (including any tautomer thereof); C_{1-4}alkoxymethyl; C_{1-4}alkoxyethyl; C_{1-2}alkyl-$S(O)_2-CH_2$-; $R^7R^8N-S(O)_2-CH_2$-; C_{1-2}alkyl-$S(O)_2-NR^{15a}-CH_2$-; $-CH_2$-OH; $-CH_2CH_2$-OH; $-CH_2-NR^7R^8$; $-CH_2-CH_2-NR^7R^8$; $-CH_2-C(O)OR^{30}$; $-CH_2-C(O)-NR^7R^8$; $-CH_2-NR^{15a}-C(O)-C_{1-3}$alkyl; $-(CH_2)_{n^{14}}-Het^1$ where n^{14} is 0 or 1; cyano (-CN); Ar^{5b}; or phenyl, pyridinyl or pyrimidinyl wherein the phenyl, pyridinyl or pyrimidinyl independently are optionally substituted by one or two of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

and/or two adjacent groups selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} are taken together and are: –CH=CH–CH=CH_2–, $-(CH_2)_{n^{14a}}-$ where n^{14a} is 3, 4 or 5 (e.g. 3 or 4), $-O-(CMe_2)-O-$, $-O-(CH_2)_{n^{14b}}-O-$ where n^{14b} is 1 or 2; $-CH=CH-NR^{15b}$-; $-N=CH-NR^{15b}$-; $-CH=N-NR^{15b}$-; $-N=N-NR^{15b}$-; -CH=CH-O-; -N=CH-O-; -CH=CH-S-; or -N=CH-S-; wherein R^{15b} is H or C_{1-2}alkyl;

provided that:

two or more of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), nitrogen (N), or nitrogen-oxide (N^+-O^-);

and no more than two of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^+-O^-),

and no more than one of A, B, D, E and F is nitrogen-oxide (N^+-O^-);

and wherein, in sub-formula (z):

G is O or S or NR^9 wherein R^9 is a hydrogen atom (H), C_{1-4}alkyl, or C_{1-2}fluoroalkyl;
J is C-R^{6J}, C-[connection point to formula (I)], or nitrogen (N),
L is C-R^{6L}, C-[connection point to formula (I)], or nitrogen (N),
M is C-R^{6M}, C-[connection point to formula (I)], or nitrogen (N),
Q is C-R^{6Q}, C-[connection point to formula (I)], or nitrogen (N),

wherein, R^{6J}, R^{6L}, R^{6M} and R^{6Q} independently are: a hydrogen atom (H), a halogen atom; C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{1-3}fluoroalkyl (e.g. C_{1-2}fluoroalkyl); C_{3-6}cycloalkyl; C_{1-4}alkoxy (e.g. C_{1-2}alkoxy); C_{1-2}fluoroalkoxy; C_{3-6}cycloalkyloxy; OH (including any tautomer thereof); or phenyl optionally substituted by one or two substituents independently being fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

provided that:
two or more of J, L, M and Q are independently C-H, C-F, C-C_{1-2}alkyl (e.g. C-Me), C-[connection point to formula (I)], or nitrogen (N);
and no more than three of J, L, M and Q are nitrogen (N);

and wherein:

R^7 and R^8 are independently a hydrogen atom (H); C_{1-4}alkyl (e.g. C_{1-2}alkyl such as methyl); C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two substituents independently being: fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

or R^7 and R^8 together are $-(CH_2)_{n^6}-$ or $-C(O)-(CH_2)_{n^7}-$ or $-C(O)-(CH_2)_{n^{10}}-C(O)-$ or $-(CH_2)_{n^8}-X^7-(CH_2)_{n^9}-$ or $-C(O)-X^7-(CH_2)_{n^{10}}-$ in which: n^6 is 3, 4, 5 or 6 (suitably n^6 is 4 or 5), n^7 is 2, 3, 4, or 5 (suitably n^7 is 3 or 4), n^8 and n^9 and n^{10} independently are 2 or 3 (suitably independently 2), and X^7 is O or NR^{14};

R^{7a} is a hydrogen atom (H) or C_{1-4}alkyl (suitably H or C_{1-2}alkyl, more suitably H or methyl);

R^{8a} is a hydrogen atom (H) or methyl (suitably H);

R^{14}, R^{17} and R^{17a} independently are: a hydrogen atom (H); C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{1-2}fluoroalkyl (e.g. CF_3); cyclopropyl; $-C(O)-C_{1-4}$alkyl (e.g. -C(O)Me);

$-C(O)NR^{7a}R^{8a}$ (e.g. $-C(O)NH_2$); or $-S(O)_2-C_{1-4}$alkyl (e.g. $-S(O)_2Me$) (preferably, R^{14}, R^{17} and/or R^{17a} independently is/are: H; C_{1-2}alkyl; or -C(O)Me);

R^{15a}, independent of other R^{15a}, is a hydrogen atom (H) or C_{1-4}alkyl (e.g. H, ^tBu or C_{1-2}alkyl such as methyl; preferably R^{15a} is H or C_{1-2}alkyl, more preferably H);

R^{16a} is:
C_{1-6}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl);
C_{3-6}cycloalkyl (e.g. C_{5-6}cycloalkyl) optionally substituted by one oxo (=O), OH or C_{1-2}alkyl substituent (e.g. optionally substituted at the 3- or 4-position of a C_{5-6}cycloalkyl ring; and/or preferably unsubstituted C_{3-6}cycloalkyl);
C_{3-6}cycloalkyl-CH_2- (e.g. C_{5-6}cycloalkyl-CH_2-);
pyridinyl (e.g. pyridin-2-yl) optionally substituted on a ring carbon atom by one of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;
Ar^{5c};
phenyl optionally substituted by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;
benzyl optionally substituted on its ring by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; or
a 4-, 5-, 6- or 7-membered saturated heterocyclic ring connected at a ring-carbon and containing one or two ring-hetero-atoms independently selected from O, S, and N; wherein any ring-nitrogens which are present are present as NR^{27} where R^{27} is H, C_{1-2}alkyl or -C(O)Me; and wherein the ring is optionally substituted at carbon by one C_{1-2}alkyl or oxo (=O) substituent, provided that any oxo (=O) substituent is substituted at a ring-carbon atom bonded to a ring-nitrogen;

R^{30}, independent of other R^{30}, is a hydrogen atom (H), C_{1-4}alkyl or C_{3-6}cycloalkyl;

Ar^{5b} and Ar^{5c} independently is/are a 5-membered aromatic heterocyclic ring containing one O, S or NR^{15a} in the 5-membered ring, wherein the 5-membered ring can optionally additionally contain one or two N atoms, and wherein the heterocyclic ring is optionally substituted on a ring carbon atom by one of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, $-CH_2OH$, $-CH_2-OC_{1-2}$alkyl, OH (including the keto tautomer thereof) or $-CH_2-NR^{28}R^{29}$ wherein R^{28} and R^{29} independently are H or methyl; and

Het^1, is a 4-, 5-, 6- or 7-membered saturated heterocyclic ring connected at a ring-carbon and containing one or two ring-hetero-atoms independently selected from O, S, and N; wherein any ring-nitrogens which are present are present as NR^{31} where R^{31} is H, C_{1-2}alkyl or -C(O)Me; and wherein the ring is optionally substituted at carbon by one

C_{1-2}alkyl or oxo (=O) substituent, provided that any oxo (=O) substituent is substituted at a ring-carbon atom bonded to a ring-nitrogen.

In compounds, for example in the compounds of formula (I) (or formula (IA) or formula (IB), see later), an "alkyl" group or moiety may be straight-chain or branched. Alkyl groups, for example C_{1-8}alkyl or C_{1-6}alkyl or C_{1-4}alkyl or C_{1-3}alkyl or C_{1-2}alkyl, which may be employed include C_{1-6}alkyl or C_{1-4}alkyl or C_{1-3}alkyl or C_{1-2}alkyl such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, or n-hexyl or any branched isomers thereof such as isopropyl, t-butyl, sec-butyl, isobutyl, 3-methylbutan-2-yl, 2-ethylbutan-1-yl, or the like.

A corresponding meaning is intended for "alkoxy", "alkylene", and like terms derived from alkyl. For example, "alkoxy" such as C_{1-6}alkoxy or C_{1-4}alkoxy or C_{1-2}alkoxy includes methoxy, ethoxy, propyloxy, and oxy derivatives of the alkyls listed above. "Alkylsulfonyl" such as C_{1-4}alkylsulfonyl includes methylsulfonyl (methanesulfonyl), ethylsulfonyl, and others derived from the alkyls listed above. "Alkylsulfonyloxy" such as C_{1-4}alkylsulfonyloxy includes methanesulfonyloxy (methylsulfonyloxy), ethanesulfonyloxy, *et al.*

"Cycloalkyl", for example C_{3-8}cycloalkyl, includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. Preferably, a C_{3-8}cycloalkyl group is C_{3-6}cycloalkyl or C_{5-6}cycloalkyl , that is contains a 3-6 membered or 5-6 membered carbocyclic ring.

"Fluoroalkyl" includes alkyl groups with one, two, three, four, five or more fluorine substituents, for example C_{1-4}fluoroalkyl or C_{1-3}fluoroalkyl or C_{1-2}fluoroalkyl such as monofluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl (CF_3CH_2-), 2,2-difluoroethyl (CHF_2CH_2-), 2-fluoroethyl (CH_2FCH_2-), etc. "Fluoroalkoxy" includes C_{1-4}fluoroalkoxy or C_{1-2}fluoroalkoxy such as trifluoromethoxy, pentafluoroethoxy, monofluoromethoxy, difluoromethoxy, etc. "Fluoroalkylsulfonyl" such as C_{1-4}fluoroalkylsulfonyl includes trifluoromethanesulfonyl, pentafluoroethylsulfonyl, etc.

A halogen atom ("halo") present in compounds, for example in the compounds of formula (I), means a fluorine, chlorine, bromine or iodine atom ("fluoro", "chloro", "bromo" or "iodo"), for example fluoro, chloro or bromo.

When the specification states that atom or moiety A is "bonded" or "attached" to atom or moiety B, it means that atom/moiety A is directly bonded to atom/moiety B usually by means of a covalent bond or a double covalent bond, and excludes A being indirectly attached to B via one or more intermediate atoms/moieties (e.g. excludes A-C-B); unless it is clear from the context that another meaning is intended.

When R^1 is C_{1-4}alkyl or C_{1-3}fluoroalkyl, it can be straight-chained or branched. Where R^1 is C_{1-4}alkyl then it can for example be methyl, ethyl, n-propyl, isopropyl or n-butyl. When R^1 is C_{1-3}fluoroalkyl, then R^1 can for example be C_1fluoroalkyl such as

monofluoromethyl, difluoromethyl, trifluoromethyl; or R^1 can be C_2fluoroalkyl such as pentafluoroethyl or more preferably C_1fluoroalkyl-CH_2- such as 2,2,2-trifluoroethyl (CF_3CH_2-), 2,2-difluoroethyl (CHF_2CH_2-), or 2-fluoroethyl (CH_2FCH_2-).

Preferably, R^1 is C_{1-3}alkyl (e.g. methyl, ethyl or n-propyl), C_{1-3}fluoroalkyl or -CH_2CH_2OH. R^1 is more preferably C_{1-3}alkyl, C_{1-2}fluoroalkyl, or -CH_2CH_2OH. Still more preferably, R^1 is C_{2-3}alkyl (e.g. ethyl or n-propyl), C_2fluoroalkyl (e.g. C_1fluoroalkyl-CH_2- such as CF_3-CH_2-) or -CH_2CH_2OH; in particular ethyl, n-propyl or -CH_2CH_2OH. Yet more preferably, R^1 is C_2alkyl or C_2fluoroalkyl. R^1 is most preferably ethyl.

Representative examples of R^1 include ethyl.

In another aspect of the invention R^2 is C_{2-4}alkyl, C_{3-5}cycloalkyl or –CH_2cyclopropyl.

Representative examples of R^2 include ethyl, propyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclopropylmethyl.

Preferably, in R^3 there is one substituent or no substituent.

In one embodiment, R^3 is the optionally substituted C_{3-8}cycloalkyl or the optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc).

In one optional embodiment, when R^3 is optionally substituted C_{3-8}cycloalkyl, it is not unsubstituted C_5cycloalkyl, i.e. not unsubstituted cyclopentyl. In this case, more suitably, R^3 is optionally substituted C_{6-8}cycloalkyl.

When R^3 is optionally substituted C_{3-8}cycloalkyl, it is more preferably optionally substituted C_{6-7}cycloalkyl or optionally substituted C_6cycloalkyl (i.e. cyclohexyl).

Suitably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) optionally substituted with one or two substituents independently being oxo (=O); OH; C_1alkoxy; C_1fluoroalkoxy (e.g. trifluoromethoxy or difluoromethoxy); NHR^{21} wherein R^{21} is a hydrogen atom (H) or C_{1-2}alkyl (more preferably R^{21} is H); C_{1-2}alkyl such as methyl; C_1fluoroalkyl such as -CH_2F or -CHF_2; -CH_2OH; -CH_2NHR^{22} wherein R^{22} is H; -C(O)OR^{23} wherein R^{23} is H or methyl; -C(O)NHR^{24} wherein R^{24} is H or methyl; -C(O)R^{25} wherein R^{25} is methyl; fluoro; hydroxyimino (=N-OH); or (C_{1-4}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-4}alkyl); and wherein any OH, alkoxy, fluoroalkoxy or NHR^{21} substituent is not substituted at the R^3

ring carbon attached (bonded) to the -NH- group of formula (I) and is not substituted at either R^3 ring carbon bonded to the Y group of the heterocyclic group (aa), (bb) or (cc).

Preferably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) optionally substituted with one or two substituents independently being oxo (=O); OH; NHR^{21} wherein R^{21} is a hydrogen atom (H); C_{1-2}alkyl such as methyl; C_1fluoroalkyl such as $-CH_2F$ or $-CHF_2$; -C(O)OR^{23} wherein R^{23} is H or methyl; -C(O)NHR^{24} wherein R^{24} is H or methyl; fluoro; hydroxyimino (=N-OH); or (C_{1-2}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-2}alkyl).

More preferably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) optionally substituted with one or two substituents independently being oxo (=O); OH; NHR^{21} wherein R^{21} is a hydrogen atom (H); methyl; $-CH_2F$; $-CHF_2$; -C(O)OR^{23} wherein R^{23} is H; -C(O)NHR^{24} wherein R^{24} is H or methyl (preferably H); fluoro; hydroxyimino (=N-OH); or methoxyimino (=N-OR^{26} where R^{26} is methyl).

Still more preferably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) optionally substituted with one or two substituents independently being oxo (=O); OH; methyl; -C(O)NHR^{24} wherein R^{24} is H; fluoro; hydroxyimino (=N-OH); or methoxyimino (=N-OR^{26} where R^{26} is methyl).

Yet more preferably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) optionally substituted with one or two substituents independently being OH; -C(O)NHR^{24} wherein R^{24} is H; oxo (=O) or hydroxyimino (=N-OH).

In one optional embodiment, in R^3, the C_{3-8}cycloalkyl can be unsubstituted.

When R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, e.g. optionally substituted C_{5-8}cycloalkyl or C_{5-7}cycloalkyl, such as optionally substituted C_6cycloalkyl (optionally substituted cyclohexyl) or optionally substituted cyclohexenyl, the one or two optional substituents if present suitably can comprise a substituent (for example is or are substituent(s)) at the 3-, 4- and/or 5-position(s), e.g. at the 3- and/or 4- position(s), of the R^3 cycloalkyl or cycloalkenyl ring.

(In this connection and generally herein, the 1-position of the R^3 ring, e.g. of the R^3 cycloalkyl or cycloalkenyl ring is deemed to be the connection point to the -NH- in formula (I) = the ring atom connecting to the -NH- in formula (I)).

Suitably, for R^3, and in particular when R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, R^3 is not substituted (other than optionally by alkyl or fluoroalkyl) at the ring atom connecting to the -NH- in formula (I), and R^3 is not substituted (other than optionally by alkyl, fluoroalkyl or NHR^{21}) at the two ring atoms either side of (bonded to) the connecting atom. For example, suitably, for R^3, and in particular when R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, R^3 is not substituted at the ring atom connecting to the -NH- in formula (I), and R^3 is not substituted at the two ring atoms either side of (bonded to) the connecting atom.

Suitably, for R^3, and in particular when R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, the one or two optional R^3 substituents if present can comprise a substituent (for example is or are substituent(s)):
(a) at the 3-position of a R^3 cyclobutyl ring, or
(b) at the 3- and/or 4- position(s) of a R^3 cyclopentyl or cyclopentenyl ring, or
(c) at the 3-, 4- and/or 5- position(s) of a R^3 cyclohexyl or cyclohexenyl ring, or
(d) at the 3-, 4-, 5- and/or 6- position(s) of a R^3 cycloheptyl or cycloheptenyl ring, or
(e) at the 3-, 4-, 5-, 6- and/or 7- position(s) of a R^3 cyclooctyl ring,
and/or
(f) at the 1-, 2- and/or highest-numbered- position(s) of a R^3 cycloalkyl or cycloalkenyl ring, for alkyl or fluoroalkyl substituent(s), and/or
(g) at the 2- and/or highest-numbered- position(s) of a R^3 cycloalkyl or cycloalkenyl ring, for NHR^{21} or fluoro substituent(s).

When R^3 is optionally substituted C_{3-8}cycloalkyl, any OH, alkoxy, fluoroalkoxy, $-CH_2CH_2OH$ or $-CH_2NHR^{22}$ substituent (particularly any OH substituent) is suitably at the 3-, 4- or 5- position, e.g. 3- or 5-position, of the R^3 cycloalkyl (e.g. C_{6-8}cycloalkyl) ring. Optionally, any OH, alkoxy, fluoroalkoxy, $-CH_2CH_2OH$ or $-CH_2NHR^{22}$ substituent (particularly any OH substituent) can be: at the 3-position of a R^3 cyclobutyl ring; or at the 3- or 4- position of a R^3 C_5cycloalkyl (cyclopentyl) ring; or at the 3-, 4- or 5- position, of a R^3 C_6cycloalkyl (cyclohexyl) ring e.g. at the 3- or 5-position of a R^3 cyclohexyl ring especially for any OH substituent; or at the 3-, 4-, 5- or 6- position of a R^3 cycloheptyl ring, or at the 3-, 4-, 5-, 6- or 7- position of a R^3 cyclooctyl ring. Suitably, any OH, alkoxy, fluoroalkoxy, $-CH_2CH_2OH$ or $-CH_2NHR^{22}$ substituent (particularly any OH substituent) is at the 3- or 4- position of a R^3 C_5cycloalkyl (cyclopentyl) ring; or more suitably at the 3-, 4- or 5- position, still more suitably at the 3- or 5-position, of a R^3 C_6cycloalkyl (cyclohexyl) ring.

Suitably, when R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, any -C(O)OR^{23}, -C(O)NHR^{24}, -C(O)R^{25} , -CH$_2$OH, or fluoro substituent is: at the 3-position of a R^3 cyclobutyl ring; or at the 3- or 4- position of a R^3 C_5cycloalkyl (cyclopentyl) or cyclopentenyl ring; or at the 3-, 4- or 5- position, preferably at the 4-position, of a R^3 C_6cycloalkyl (cyclohexyl) or cyclohexenyl ring; or at the 3-, 4-, 5- or 6- position of a R^3 cycloheptyl or cycloheptenyl ring, or at the 3-, 4-, 5-, 6- or 7- position of a R^3 cyclooctyl ring. Any -C(O)OR^{23}, -C(O)NHR^{24}, -C(O)R^{25} , -CH$_2$OH, or fluoro substituent, e.g. any -C(O)NHR^{24} or fluoro substituent, is suitably at the 3-, 4- or 5- position, more suitably at the 4-position, of a R^3 C_6cycloalkyl (cyclohexyl) or cyclohexenyl ring. It is particularly preferable for any –C(O)NHR^{24} substituent to be at the 4-position of a R^3 cyclohexyl ring.

When R^3 is optionally substituted C_{3-8}cycloalkyl, any NHR^{21} substituent is at any position other than the 1-position (the ring atom connecting to the -NH- in formula (I)), e.g. at the 3-, 4-, 5-, 6-, 7- or 8- position. Preferably, any NHR^{21} substituent is at the 2-, 3-, 5- or 6- position, or more preferably at the 3- or 5- position, of a R^3 cyclohexyl ring.

When R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, any alkyl or fluoroalkyl substituent can for example be at the 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8- position, for example at the 1-, 2-, 3-, 5- or 6- position, e.g. the 1-position, of the R^3 ring. Preferably, any alkyl or fluoroalkyl substituent is at the 1-, 2-, 3-, 5- or 6- position, or more preferably at the 1-, 3- or 5- position, of a R^3 cyclohexyl or cyclohexenyl ring.

When R^3 is optionally substituted C_{3-8}cycloalkyl, any oxo (=O), hydroxyimino (=N-OH); or (C_{1-4}alkoxy)imino (=N-OR^{26}) substituent is suitably at the 3-, 4- or 5- position, e.g. at the 4-position, of the R^3 cycloalkyl (e.g. C_{6-8}cycloalkyl e.g. cyclohexyl) ring. Preferably any such substituent is at the 4-position of a R^3 cyclohexyl ring.

When R^3 is optionally substituted C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl), R^3 is preferably cyclohexyl (i.e. unsubstituted); or cycloheptyl (i.e. unsubstituted); or cyclohexyl substituted by one substituent being oxo (=O), OH, NHR^{21}, C_{1-2}alkyl, C_{1-2}fluoroalkyl, -CH$_2$OH, -C(O)OR^{23}, -C(O)NHR^{24}, -C(O)R^{25}, fluoro, hydroxyimino (=N-OH), or (C_{1-4}alkoxy)imino (=N-OR^{26}); or cyclohexyl substituted by two fluoro substituents. More preferably, R^3 is cyclohexyl (i.e. unsubstituted); or cycloheptyl (i.e. unsubstituted); or cyclohexyl substituted by one substituent being oxo (=O), OH, NHR^{21}, C_{1-2}alkyl, C_{1-2}fluoroalkyl, -C(O)OR^{23}, -C(O)NHR^{24}, fluoro, hydroxyimino (=N-OH), or (C_{1-2}alkoxy)imino (=N-OR^{26} wherein R^{26} is C_{1-2}alkyl); or cyclohexyl substituted by

two fluoro substituents. Still more preferably R^3 is cyclohexyl (i.e. unsubstituted) or cyclohexyl substituted by one oxo (=O), hydroxyimino (=N-OH), -C(O)NH_2, methyl or OH substituent. The optional substituent can for example be at the 3- or 4- position, of the R^3 cyclohexyl ring. Preferably, any OH substituent is preferably at the 3-position of a R^3 cyclohexyl ring, and/or any oxo (=O), hydroxyimino (=N-OH), (C_{1-4}alkoxy)imino (=N-OR^{26}) or -C(O)NH_2 substituent is preferably at the 4-position of a R^3 cyclohexyl ring, and/or any alkyl or fluoroalkyl substituent is preferably at the 1-, 3- or 5- position of a R^3 cyclohexyl ring.

When R^3 is optionally substituted C_{6-7}cycloalkyl, R^3 can for example be 4-hydroxy-cyclohexyl (i.e. 4-hydroxycyclohexan-1-yl), 4-methylcyclohexyl, 3-fluorocyclohexyl, 2-aminocyclohexyl, 3-(HO(O)C)cyclohexyl or 3-oxocyclohexyl, but R^3 is more preferably cyclohexyl (i.e. unsubstituted), cycloheptyl (i.e. unsubstituted), 3-hydroxy-cyclohexyl (i.e. 3-hydroxycyclohexan-1-yl) (e.g. in a *cis* configuration), 4-oxo-cyclohexyl (i.e. 4-oxocyclohexan-1-yl), 4-(hydroxyimino)cyclohexyl (i.e. 4-(hydroxyimino)cyclohexan-1-yl), 4-(C_{1-2}alkoxyimino)cyclohexyl, 4-(aminocarbonyl)cyclohexyl (i.e. 4-(aminocarbonyl)cyclohexan-1-yl) (e.g. in a *cis* configuration), 1-methylcyclohexyl, 3-methylcyclohexyl, 4,4-(difluoro)cyclohexyl, or 3-aminocyclohexyl.

When R^3 is optionally substituted C_{6-7}cycloalkyl, R^3 is most preferably cyclohexyl (i.e. unsubstituted), 3-hydroxy-cyclohexyl (i.e. 3-hydroxycyclohexan-1-yl) (e.g. in a *cis* configuration), 4-oxo-cyclohexyl (i.e. 4-oxocyclohexan-1-yl), 4-(hydroxyimino)cyclohexyl (i.e. 4-(hydroxyimino)cyclohexan-1-yl), or 4-(aminocarbonyl)cyclohexyl (i.e. 4-(aminocarbonyl)cyclohexan-1-yl) (e.g. in a *cis* configuration).

When R^3 is optionally substituted C_5cycloalkyl (optionally substituted cyclopentyl), R^3 can for example be cyclopentyl (i.e. unsubstituted) or more suitably 3-hydroxy-cyclopentyl.

When R^3 is optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl, preferably it is optionally substituted mono-unsaturated-C_{5-6}cycloalkenyl, more preferably optionally substituted mono-unsaturated-C_6cycloalkenyl (i.e. optionally substituted mono-unsaturated-cyclohexenyl = optionally substituted cyclohexenyl). For example, the R^3 cyclohexenyl can be optionally substituted cyclohex-3-en-1-yl.

When R^3 is optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl, in one optional embodiment the R^3 cycloalkenyl is optionally substituted with one or two substituents independently being fluoro or methyl. Preferably, in this embodiment, if there are two substituents then they are not both methyl.

In another optional embodiment, the R^3 cycloalkenyl (e.g. cyclohexenyl) is optionally substituted with one substituent being fluoro or C_{1-2}alkyl (preferably fluoro or methyl); more preferably the R^3 cycloalkenyl (e.g. cyclohexenyl) is substituted with one fluoro substituent or is unsubstituted. For example, the R^3 optionally substituted cycloalkenyl can be cyclohex-3-en-1-yl (i.e. unsubstituted) or 4-fluoro-cyclohex-3-en-1-yl.

For R^3 cycloalkenyl, the optional substituent(s) can for example be at the 1-, 2-, 3-, 4-, 5- or 6- position(s) of the cycloalkenyl ring.

When R^3 is the heterocyclic group of sub-formula (aa), (bb) or (cc), then Y is preferably O or NR^{10}, most preferably O.

Suitably, R^{10} is a hydrogen atom (H), methyl, ethyl, $C(O)NH_2$, C(O)-C_{1-2}alkyl or C(O)-C_1fluoroalkyl. . Preferably, R^{10} is not C_{1-2}alkyl or C_{1-2}fluoroalkyl. Suitably R^{10} is not $CH_2C(O)NH_2$.

More preferably, R^{10} is a hydrogen atom (H), $C(O)NH_2$, C(O)-C_{1-2}alkyl (e.g. C(O)methyl) or C(O)-C_1fluoroalkyl (e.g. C(O)-CF_3). Still more preferably R^{10} is H, $C(O)NH_2$ or C(O)methyl; for example $C(O)NH_2$.

When R^3 is the heterocyclic group of sub-formula (aa), (bb) or (cc), then it is preferable that R^3 is the heterocyclic group of sub-formula (aa) or (bb), more preferably of sub-formula (bb).

In sub-formula (bb), n^1 is preferably 1. In sub-formula (cc), n^2 is preferably 1. That is, six-membered rings are preferred in the R^3 heterocyclic group.

Suitably, in R^3, the heterocyclic group of sub-formula (aa), (bb) or (cc) is unsubstituted on a ring carbon. (In this connection, where Y is NR^{10}, R^{10} is not a substituent on a ring carbon).

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), the one or two optional substituents preferably comprise (e.g. is or independently are) OH; oxo (=O); C_{1-2}alkyl (e.g. methyl) or C_{1-2}fluoroalkyl (e.g. C_1fluoroalkyl such as -CH_2F or -CHF_2). More preferably, in the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), the one or two optional substituents comprise (e.g. is or independently are) C_{1-2}alkyl (e.g. methyl) or oxo; most preferably the one or two optional substituents comprise (e.g. is or are) oxo (=O).

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), any oxo (=O) substituent is preferably on a carbon atom bonded (adjacent) to Y, e.g. is on a carbon atom bonded (adjacent) to Y only when Y is O or NR^{10}.

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), any oxo (=O) substituent can suitably be at the 2-, 3-, 4-, 5- or 6- position of the R^3 heterocyclic ring. For example any oxo (=O) substituent(s) can be: at the 2-, 4- or 5- position(s) (e.g. 2-position or 4-position, or two oxo substituents at 2- and 4- positions) of a R^3 heterocyclic group of sub-formula (aa), at the 2-, 4-, 5- or 6- position(s) (e.g. 4-position) of a six-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 1, at the 2-, 3-, 5-, 6- or 7-position(s) (e.g. 5-position) of a seven-membered R^3 heterocyclic group of sub-formula (bb) wherein n^1 is 2, or at the 2-, 4-, 5-, 6- or 7- position(s) (e.g. 2-position) of a seven-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 2.

(In this connection and generally herein, the 1-position of the R^3 heterocyclic ring is deemed to be the connection point to the -NH- in formula (I) = the ring atom connecting to the -NH- in formula (I), and the remaining positions of the ring are then numbered so that the ring heteroatom takes the lowest possible number).

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), any alkyl or fluoroalkyl substituent can for example be at the 1-, 2-, 3-, 4-, 5- or 6- position, e.g. the 1-position, of the R^3 heterocyclic ring, for example at the 1-, 3- or 5- position of a six-membered R^3 heterocyclic ring.

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), any OH substituent can be: at the 5-position of a six-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 1; at the 5- or 6- position of a seven-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 2; or at the 6- position of a seven-membered R^3 heterocyclic group of sub-formula (bb) wherein n^1 is 2.

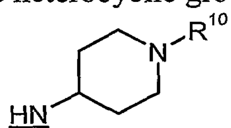
Any other substituents of the R^3 heterocyclic group can optionally be positioned on the R^3 heterocyclic ring at numerical positions as described herein for when R^3 is optionally substituted C_{5-7}cycloalkyl, all necessary changes to the wording being made.

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), preferably, only C_{1-2}alkyl, C_{1-2}fluoroalkyl, fluoro or oxo (=O) substitution or no substitution is allowed independently at each of the 2- and highest-numbered- positions of the R^3 heterocyclic ring (e.g. at each of the 2- and 6- positions of a six-membered R^3 heterocyclic ring), and/or only C_{1-2}alkyl, C_{1-2}fluoroalkyl or fluoro substitution or no substitution is allowed at the 1-position of the R^3 heterocyclic ring.

When R^3 is the heterocyclic group of sub-formula (aa) and Y is NR^{10}, then R^{10} is not C(O)-C_{1-2}alkyl, C(O)-C_1fluoroalkyl or -C(O)-CH_2O-C_{1-2}alkyl. According to one optional embodiment when R^3 is the heterocyclic group of sub-formula (aa) and Y is

NR^{10} then R^{10} is optionally not C(O)NHMe, C(O)-C_{1-2}alkyl, C(O)-C_1fluoroalkyl or -C(O)-CH_2O-C_{1-2}alkyl.

In one preferable embodiment, Y is O, S, SO_2 or NH when R^3 is the heterocyclic group of sub-formula (aa).

When R^3 is the heterocyclic group of sub-formula (bb), n^1 is 1, and Y is NR^{10} (e.g. when NHR^3 is ), then R^{10} is not C_{1-2}alkyl or C_{1-2}fluoroalkyl. More preferably, when R^3 is the heterocyclic group of sub-formula (bb) wherein n^1 is 1 or 2 and Y is NR^{10}, then R^{10} is preferably not C_{1-2}alkyl or C_{1-2}fluoroalkyl.

In one embodiment, when R^3 is the heterocyclic group of sub-formula (bb), then preferably Y is O, S, SO_2 or NR^{10} wherein R^{10} is H, C(O)NH_2, C(O)-C_{1-2}alkyl (e.g. C(O)methyl) or C(O)-C_1fluoroalkyl (e.g. C(O)-CF_3), or more preferably R^{10} is H, C(O)NH_2 or C(O)Me, for example C(O)NH_2 or C(O)Me most preferably $CONH_2$.

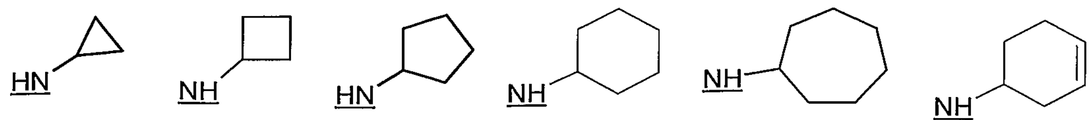
In one optional embodiment, when R^3 is the heterocyclic group of sub-formula (cc), then optionally Y is O, S, SO_2 or NR^{10} wherein R^{10} is H, C(O)NH_2, C(O)-C_{1-2}alkyl (e.g. C(O)methyl) or C(O)-C_1fluoroalkyl (e.g. C(O)-CF_3). In this case R^{10} can for example be H, C(O)NH_2 or C(O)Me, for example H.

Optionally, for sub-formula (bb) and/or for sub-formula (cc), Y is O or NR^{10}.

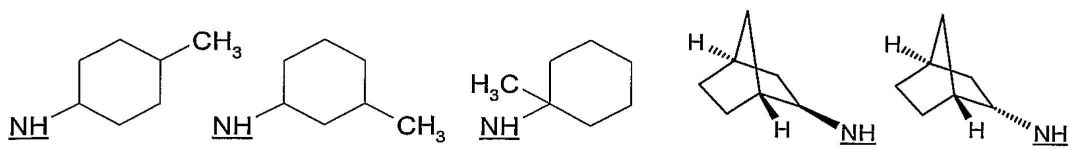
When R^3 is optionally substituted C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) or optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc), then a substituent can be in the *cis* or *trans* configuration with respect to the -NH- group of formula (I) to which R^3 is attached (bonded); this includes mixtures of configurations wherein the stated configuration is the major component. For example, an OH or -C(O)NHR^{24} substituent on C_{6-7}cycloalkyl can for example be in the *cis* configuration and/or a NHR^{21} substituent on C_{6-7}cycloalkyl can for example be in the *cis* or *trans* configuration, with respect to the -NH- group of formula (I) to which R^3 is attached (bonded), including mixtures of configurations wherein the stated configuration is the major component.

When R^3 is a bicyclic group of sub-formula (ee), then preferably Y^1, Y^2 and Y^3 are all CH_2.

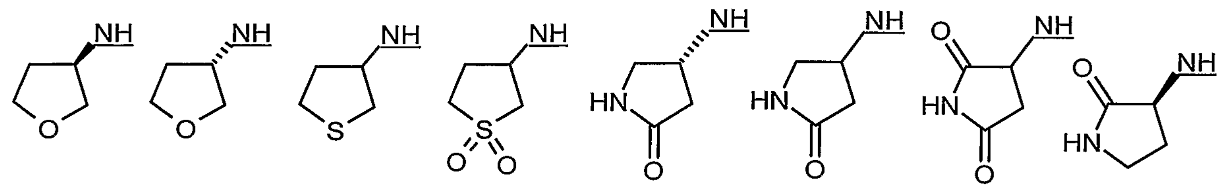
Preferably, NHR^3 is of sub-formula (a), (a1), (b), (c), (c 1), (c 2), (c 3), (c 4), (c 5), (c 6), (c 7), (d), (e), (f), (g), (g1), (g2), (g3), (g4), (h), (i), (j), (k), (k1), (k2), (L), (m), (m1), (m2), (m3), (m5), (n), (o), (o1), (o2), (o3), (p), (p1), (p2), (p3), (p4), (p5), (p6), (p7), (p8), (p9), (p10), (p11) or (q):



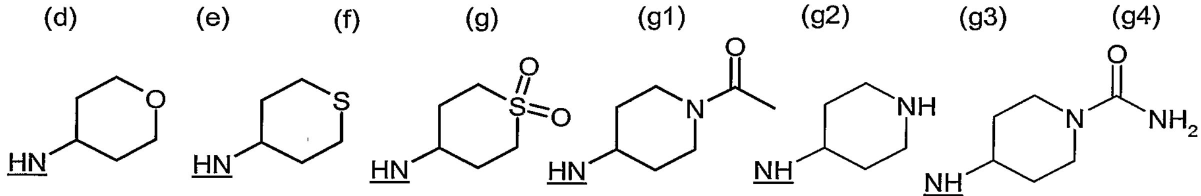
(a) (a1) (b) (c) (c 1) (c 2)



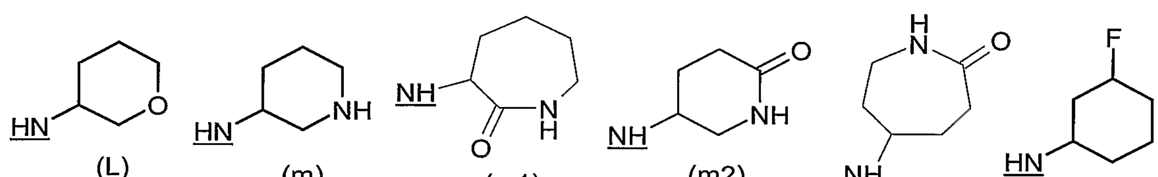
(c 3) (c 4) (c 5) (c 6) (c 7)



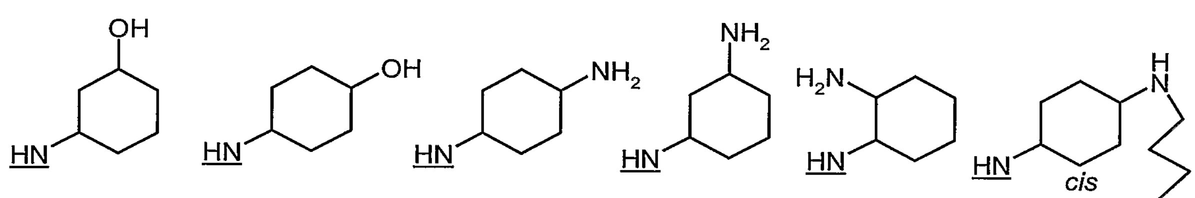
(d) (e) (f) (g) (g1) (g2) (g3) (g4)



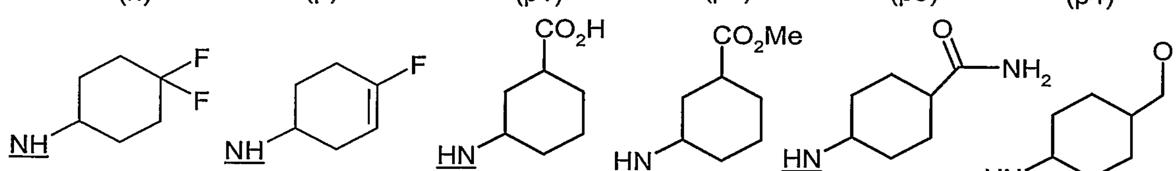
(h) (i) (j) (k) (k1) (k2)



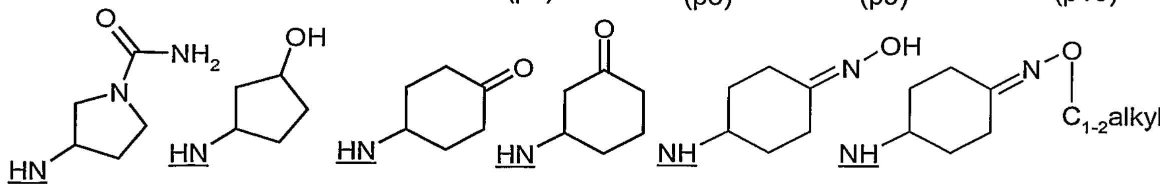
(L) (m) (m1) (m2) (m3) (m5)



(n) (p) (p1) (p2) (p3) (p4)



(p5) (p6) (p7) (p8) (p9) (p10)

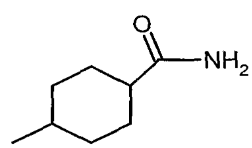


(p11) (q) (o) (o1) (o2) (o3)

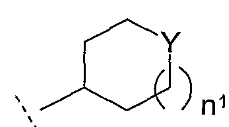
In the sub-formulae (a) to (q) etc above, the -NH- connection point of the NHR^3 group to the 4-position of the pyrazolopyridine of formula (I) is underlined.

Preferably, NHR^3 is of sub-formula (c), (c1), (c 2), (c 3), (c 4), (c 5), (c 6), (c 7), (d), (e), (f), (g1), (g4), (h), (i), (j), (k), (k1), (k2), (L), (m), (m1), (m2), (m3), (m5), (n), (o), (o1), (o2), (o3), (p), (p2), (p5), (p6), (p7), (p9), (p10), (p11) or (q). More preferably, NHR^3 is of sub-formula (c), (c1), (c 4), (c 5), (h), (i), (j), (k), (k2), (m1), (m2), (n), (o), (o2), (o3), (p2), (p5), (p6), (p9), (p11) or (q). NHR^3 can for example be of sub-formula (c), (p11), (h), (k), (k2), (n), (o), (o2) or (p9); or still more preferably (c), (p11), (h), (k2), (n), (o), (o2) or (p9). Most preferably, R^3 is tetrahydro-2H-pyran-4-yl or 1-(aminocarbonyl)-4-piperidinyl; that is NHR^3 is most preferably of sub-formula (h) or (k2), as shown above.
In another aspect of the invention R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) optionally substituted with one or two substituents independently being oxo (=O); OH; methyl; $-C(O)NHR^{24}$ wherein R^{24} is H; fluoro; hydroxyimino (=N-OH); or methoxyimino ($=N-OR^{26}$ where R^{26} is methyl).

In another aspect of the invention R^3 is a 4-(aminocarbonyl)cyclohexyl (i.e. 4-(aminocarbonyl)cyclohexan-1-yl) group of sub-formula (aa), or an N-aminocarbonyl-piperidinyl or an N-aminocarbonyl-pyrrolidinyl or a tetrahydropyranyl group of sub-formula (bb);



(aa)



(bb)

wherein Y is O or $NCONH_2$ and n^1 is 0 or 1;

and wherein the cyclohexyl group of sub-formula (aa) or the piperidinyl, pyrrolidinyl or tetrahydropyranyl groups of sub-formula (bb) may be further optionally substituted with one or two substituents independently selected from C_{1-2}alkyl; C_{1-2}fluoroalkyl; CH_2OH; $-C(O)OR^{23}$ wherein R^{23} is H or C_{1-2}alkyl; $-C(O)NHR^{23}$; or fluoro; on any ring carbon; as well as, on the C2, C3, C5 and C6 of the cyclohexyl group of (aa), the C2 or C6 of the piperidinyl ring or the C5 of the pyrrolidinyl ring of (bb), a substituent selected from OH; C_{1-2}alkoxy; C_{1-2}fluoroalkoxy; or alkoxy.

Representative examples of R^3 include tetrahydro-2H-pyran-4-yl.

When NHR^3 is of sub-formula (n), then preferably it is in the *cis* configuration, i.e. preferably it is a *cis*-(3-hydroxycyclohexan-1-yl)amino group, e.g. in any enantiomeric form or mixture of forms such as a racemic mixture.

When NHR^3 is of sub-formula (p9), then preferably it is in the *cis* configuration, i.e. preferably it is a *cis*-[4-(aminocarbonyl)cyclohexan-1-yl]amino group.

Where R^4 is C_{1-2}fluoroalkyl, then it can be C_1fluoroalkyl such as monofluoromethyl, difluoromethyl or trifluoromethyl.

R^{4a} can suitably be a hydrogen atom (H) or methyl (Me), more suitably H.

R^4 can for example be a hydrogen atom (H); methyl, ethyl, C_1fluoroalkyl, $-CH_2OH$, $-CH(Me)OH$, $-CH_2CH_2OH$, or $-CH_2OMe$; or preferably a hydrogen atom (H), methyl, ethyl, $-CH_2OH$, or $-CH_2OMe$. More preferably, R^4 is H, methyl, ethyl, $-CH_2OH$, or $-CH_2OMe$.

Representative examples of R^4 include H, methyl and ethyl.

In another aspect of the invention, R^5 is a hydrogen atom (H), methyl, ethyl, n-propyl, or iso-propyl.

Representative examples of R^5 include H.

In another aspect of the invention, in sub-formulae (y) and (y1) m is 1, A is $C\text{-}R^{6A}$, B is $C\text{-}R^{6B}$, D is $C\text{-}R^{6D}$ and E is $C\text{-}R^{6E}$.

Representative examples of (y) include 2,3-dihydro-1H-inden-2-yl.

It is preferable that Ar has the sub-formula (x).

Preferably, in sub-formula (x), two or more (more preferably three or more) of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine) or nitrogen (N).

Preferably, in sub-formula (x), three or more of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), nitrogen (N), or nitrogen-oxide ($N^+\text{-}O^-$).

Preferably, in sub-formula (x), two or more (e.g. three or more) of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), or nitrogen (N); and one or more (e.g. two or more) others of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), C-Cl (carbon-chlorine), C-Me, C-OMe, or nitrogen

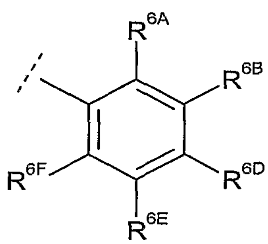
(N). More preferably, in sub-formula (x), two or more (e.g. three or more) of A, B, D, E and F are C-H (carbon-hydrogen); and one or more (e.g. two or more) others of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), C-Cl (carbon-chlorine), C-Me, C-OMe, or nitrogen (N).

Preferably, in sub-formula (x), two or more (e.g. three or more, e.g. four or more) of A, B, D, E and F are C-H.

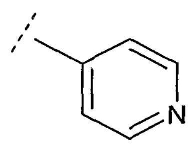
Preferably, in sub-formula (x), no more than one (more preferably none) of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^{+}-O^{-}).

Preferably, in sub-formula (x), none of A, B, D, E and F are nitrogen-oxide (N^{+}-O^{-}).

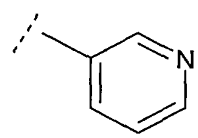
Preferably, Ar has the sub-formula (x) which is sub-formula (x1), (x2), (x3), (x4), (x5), (x6), (x7), (x8), (x9), (x10), (x11), (x12), (x13), (x14), (x15) or (x16):



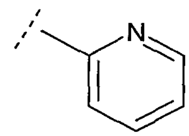
(x1)



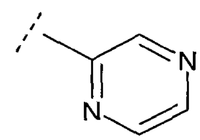
(x2)



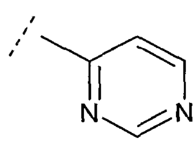
(x3)



(x4)



(x5)



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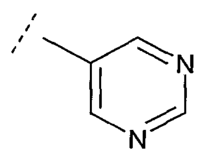
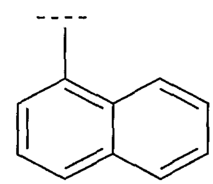


(x7)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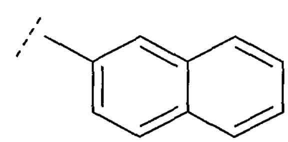
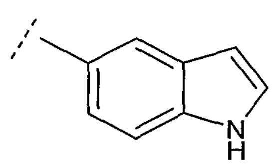
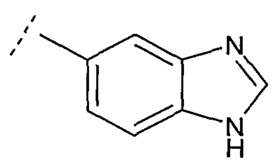
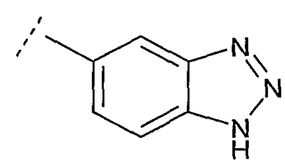

(x9)



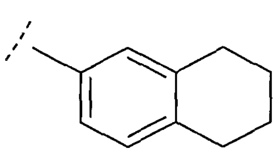
(x10)



(x11)



(x12)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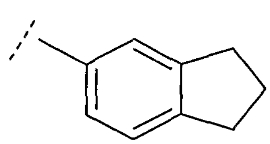
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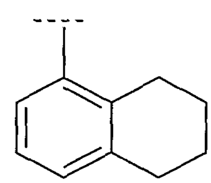
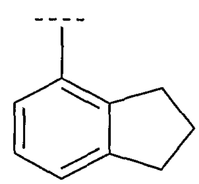

(x15)


(x16)

More preferably, Ar has the sub-formula (x) which is sub-formula (x1), (x2), (x3), (x8), (x13), or (x14). Still more preferably, Ar has the sub-formula (x) which is sub-formula (x1), (x8), (x13), or (x14). Most preferably, Ar has the sub-formula (x) which is sub-formula (x1).

In sub-formula (x), preferably, R^{6A}, R^{6B}, R^{6D}, R^{6E} and/or R^{6F}, independently of each other, is or are: a hydrogen atom (H), a fluorine, chlorine, bromine or iodine atom, methyl, ethyl, n-propyl, isopropyl, C_4alkyl, trifluoromethyl, $-CH_2OH$, methoxy, ethoxy, n-propoxy, isopropoxy, C_1fluoroalkoxy (e.g. trifluoromethoxy or difluoromethoxy), cyclohexyloxy; cyclopentyloxy; nitro ($-NO_2$), OH, C_{1-3}alkylS(O)$_2$- (such as MeS(O)$_2$-), C_{1-3}alkylS(O)$_2$-NH- such as Me-S(O)$_2$-NH-, Me_2N-S(O)$_2$-, H_2N-S(O)$_2$-, $-CONH_2$, -CONHMe, -C(O)OH, cyano (-CN), NMe_2, or C_{1-2}alkyl-S(O)$_2$-CH_2- such as Me-S(O)$_2$-CH_2-.

More preferably, R^{6A}, R^{6B}, R^{6D}, R^{6E} and/or R^{6F}, independently of each other, is or are: a hydrogen atom (H), a fluorine, chlorine, bromine or iodine atom, methyl, ethyl, n-propyl, isopropyl, isobutyl, trifluoromethyl, $-CH_2OH$, methoxy, ethoxy, n-propoxy, isopropoxy, C_1fluoroalkoxy (e.g. trifluoromethoxy or difluoromethoxy), nitro ($-NO_2$), OH, C_{1-3}alkylS(O)$_2$- such as MeS(O)$_2$-, C_{1-2}alkylS(O)$_2$-NH- such as Me-S(O)$_2$-NH-, $-CONH_2$, cyano (-CN), or C_{1-2}alkylS(O)$_2$-CH_2- such as Me-S(O)$_2$-CH_2.

Still more preferably, R^{6A}, R^{6B}, R^{6D}, R^{6E} and/or R^{6F}, independently of each other, is or are: a hydrogen atom (H), a fluorine, chlorine or bromine atom, methyl, ethyl, n-propyl, isopropyl, trifluoromethyl, $-CH_2OH$, methoxy, ethoxy, n-propoxy, difluoromethoxy, OH or MeS(O)$_2$-.

When two adjacent groups selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} are taken together, then, preferably, when taken together they are: $-CH=CH-CH=CH_2-$, $-(CH_2)_n{}^{14a}-$ where n^{14a} is 3, 4 or 5 (e.g. 3 or 4), $-O-(CMe_2)-O-$, $-O-(CH_2)_n{}^{14b}-O-$ where n^{14b} is 1 or 2; $-CH=CH-NR^{15b}-$; $-N=CH-NR^{15b}-$; $-N=N-NR^{15b}$ wherein R^{15b} is H or C_{1-2}alkyl (preferably R^{15b} is H). More preferably, in this embodiment, two adjacent groups selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} are taken together and are: $-CH=CH-CH=CH_2-$ or $-(CH_2)_n{}^{14a}-$ where n^{14a} is 3, 4 or 5 (e.g. 3 or 4).

In sub-formula (x), e.g. in sub-formula (x1), suitably, one, two or three of R^{6B}, R^{6D} and R^{6E} are other than a hydrogen atom (H).

In sub-formula (x), e.g. in sub-formula (x1), preferably, one or both of R^{6A} and R^{6F} are independently a hydrogen atom (H), a fluorine atom (F), or methyl. For example, one or both of R^{6A} and R^{6F} can be a hydrogen atom (H).

In sub-formula (x), e.g. in sub-formula (x1), suitably the ring or ring system is unsubstituted, monosubstituted, disubstituted or trisubstituted, preferably the ring or ring system is monosubstituted or disubstituted. In sub-formula (x), e.g. in sub-formula (x1), for monosubstitution of the ring or ring system, then the one substituent selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} is suitably present at the 3- or 4-position with respect to the $-(CR^4R^5)-$ side-chain (i.e. D is CR^{6D} where R^{6D} is other than H), or is a 2-methyl 2-ethyl, 2-fluoro or 2-chloro substituent. In sub-formula (x), e.g. in sub-formula (x1), for disubstitution of the ring or ring system, then 3,4-disubstitution, 2,4-disubstitution, 2,3-disubstitution or 3,5-disubstitution is suitable.

In one preferable embodiment, Ar has the sub-formula (x1) and is: phenyl, monoalkyl-phenyl-, mono(fluoroalkyl)-phenyl-, monohalo-phenyl-, monoalkoxy-phenyl-, mono(fluoroalkoxy)-phenyl-, mono(N,N-dimethylamino)-phenyl-, mono(methyl-SO_2-NH-)-phenyl-, mono(methyl-SO_2-)-phenyl-, dialkyl-phenyl-, monoalkyl-monohalo-phenyl-, mono(fluoroalkyl)-monohalo-phenyl-, dihalo-phenyl-, dihalo-monoalkyl-phenyl-, dihalo-mono(hydroxymethyl)-phenyl- (e.g. 2,3-dichloro-6-(hydroxymethyl)-phenyl-), or dialkoxy-phenyl- such as 3,4-dimethoxy-phenyl-. The substituents can preferably be further defined, as defined in preferable embodiments herein.

In one preferable embodiment, Ar is of sub-formula (x1) and is: monoalkyl-phenyl-, mono(fluoroalkyl)-phenyl-, monohalo-phenyl-, monoalkoxy-phenyl-, mono(fluoroalkoxy)-phenyl-, dialkyl-phenyl-, monoalkyl-monohalo-phenyl-, dihalo-phenyl- or dihalo-monoalkyl-phenyl-.

More preferably, in this embodiment, Ar is:
- monoC_{1-4}alkyl-phenyl- or monoC_{1-3}alkyl-phenyl- such as 4-C_{1-4}alkyl-phenyl- (e.g. 4-C_{1-3}alkyl-phenyl-) or 2-C_{1-2}alkyl-phenyl-;
- monoC_1fluoroalkyl-phenyl- such as 4-C_1fluoroalkyl-phenyl-;
- monoC_{1-3}alkoxy-phenyl- such as 4-C_{1-3}alkoxy-phenyl- or 3-C_{1-3}alkoxy-phenyl-;
- mono(C_1fluoroalkoxy)-phenyl- such as 4-C_1fluoroalkoxy-phenyl-;
- diC_{1-3}alkyl-phenyl- or diC_{1-2}alkyl-phenyl- or dimethyl-phenyl- such as 3,4-dimethyl-phenyl-, 2,4-dimethyl-phenyl-, 3,5-dimethyl-phenyl-, 2,3-dimethyl-phenyl- or 2,5-dimethyl-phenyl-; for example 3,4-dimethyl-phenyl-, 2,4-dimethyl-phenyl-, 2,3-dimethyl-phenyl- or 3,5-dimethyl-phenyl-;
- monoC_{1-3}alkyl-monohalo-phenyl-, such as monoC_{1-2}alkyl-monohalo-phenyl- and/or monoC_{1-3}alkyl-monochloro-phenyl- or monoC_{1-3}alkyl-monofluoro-phenyl-, for example 4-methyl-3-chloro-phenyl-, 3-methyl-4-chloro-phenyl-, or 2-methyl-4-chloro-phenyl-;
- dihalo-phenyl- such as 2-chloro-4-fluorophenyl- or 2,4-difluoro-phenyl- or 4-bromo-2-fluorophenyl- or preferably 4-chloro-2-fluorophenyl-; for example dichloro-phenyl-

such as 3,4-dichloro-phenyl- or 2,4-dichloro-phenyl- or 2,6-dichloro-phenyl- or preferably 2,3-dichloro-phenyl-; or
- dihalo-monoC_{1-2}alkyl-phenyl- e.g. 2,4-dichloro-6-methyl-phenyl-.

In an alternative embodiment, Ar has the sub-formula (z).

Preferably, in sub-formula (z), three or more (for example all) of J, L, M and Q are independently C-H, C-F, C-C_{1-2}alkyl (e.g. C-Me), C-[connection point to formula (I)], or nitrogen (N).

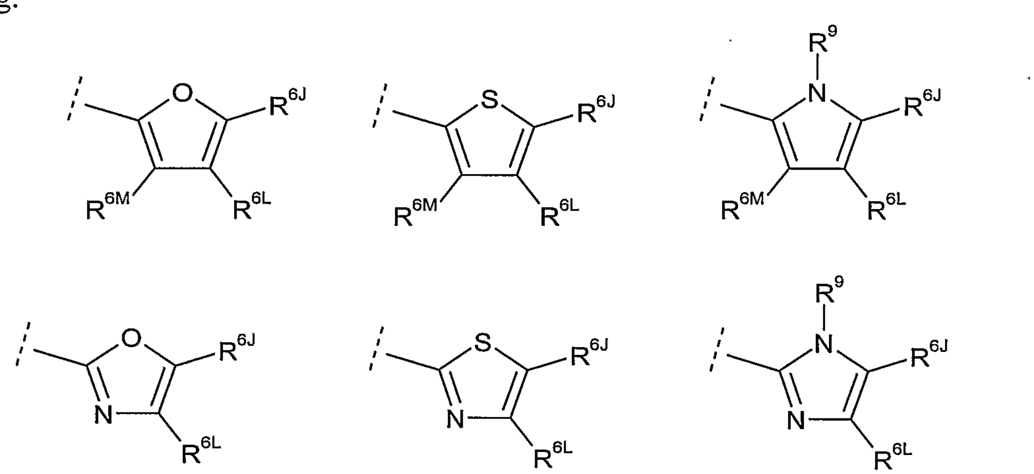
Preferably, in sub-formula (z), no more than two (for example no more than one) of J, L, M and Q are nitrogen (N).

Suitably, Q is C-[connection point to formula (I)].

Suitably, R^9 is a hydrogen atom (H) or methyl.

Suitably, R^{6J}, R^{6L}, R^{6M} and/or R^{6Q} independently is or are: a hydrogen atom (H); fluoro; chloro; C_{1-2}alkyl (e.g. methyl); C_1fluoroalkyl (e.g. CF_3); C_{1-2}alkoxy (methoxy); C_1fluoroalkoxy (e.g. CF_2HO-); OH (including any tautomer thereof); or phenyl optionally substituted by one substituent being fluoro, methyl, C_1fluoroalkyl, methoxy or C_1fluoroalkoxy. More SuitablyR^{6J}, R^{6L}, R^{6M} and/or R^{6Q} independently is or are H, OH (including any keto tautomer thereof), or more preferably C_{1-2}alkyl (e.g. methyl) or C_1fluoroalkyl.

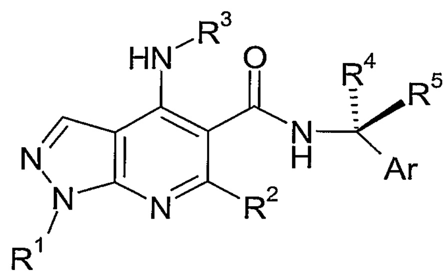
When Ar has the sub-formula (z), then sub-formula (z) can suitably be one of the following:



In another aspect of the invention Ar is phenyl and $R6^A$, $R6^B$, $R6^D$, $R6^E$ and $R6^F$ are independently H, C_{1-2}alkyl, C_{1-2}alkoxy or halogen.

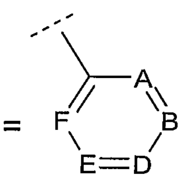
Representative examples of Ar include 4-chloro-2-methylphenyl, 4-methoxyphenyl, 3,4-dimethylphenyl, 4-chlorophenyl, and phenyl.

Preferably, the compound of formula (I) or the salt thereof is a compound of formula (IA) or a salt thereof:



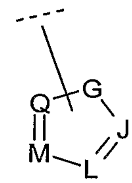
(IA)

wherein Ar =



(x)

or



(z) ,

Formula (IA) means that more than 50% of the compound or salt present has the stereochemistry shown at the carbon atom bearing the R^4 and R^5 groups.

Preferably, the stereochemistry at the carbon atom bearing the R^4 and R^5 groups is such that there is an enantiomeric excess (e.e.) of 50% or more at the carbon atom bearing the R^4 and R^5 groups (ignoring the stereochemistry at any other carbon atoms). More preferably, the enantiomeric excess (e.e.) is 70% or more or 80% or more, still more preferably 90% or more, yet more preferably 95% or more, at the carbon atom bearing the R^4 and R^5 groups (ignoring the stereochemistry at any other carbon atoms).

"Enantiomeric excess" (e.e.) is defined as the percentage of the major isomer present minus the percentage of the minor isomer present. For example, if 95% of major isomer is present and 5% of the minor isomer is present, then the e.e. would be 90%.

In another aspect of the invention in formula (IA) R^4 is not a hydrogen atom (H). In this aspect in formula (IA), R^4 can for example be methyl, ethyl, C_1 fluoroalkyl (such as CF_3), $-CH_2OH$, or $-CH_2OMe$.

In another aspect of the invention in formula (IA) R^5 is a hydrogen atom (H) and R^4 is not a hydrogen atom (H).

It is particularly preferred that the compound of formula (I) or the salt thereof is:

N-[(4-chloro-2-methylphenyl)methyl]-6-cyclopropyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-cyclopropyl-1-ethyl-N-(phenylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-cyclopropyl-1-ethyl-N-{[4-(methyloxy)phenyl]methyl}-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-cyclopropyl-N-[(3,4-dimethylphenyl)methyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[1-(4-chlorophenyl)ethyl]-6-cyclopropyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[1-(4-chlorophenyl)propyl]-6-cyclopropyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
1-ethyl-N-(phenylmethyl)-6-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
1-ethyl-N-{[4-(methyloxy)phenyl]methyl}-6-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(4-chloro-2-methylphenyl)methyl]-1-ethyl-6-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(3,4-dimethylphenyl)methyl]-1-ethyl-6-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-(2,3-dihydro-1H-inden-2-yl)-1-ethyl-6-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
1,6-diethyl-N-(phenylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
1,6-diethyl-N-{[4-(methyloxy)phenyl]methyl}-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(3,4-dimethylphenyl)methyl]-1,6-diethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-(2,3-dihydro-1H-inden-2-yl)-1,6-diethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[1-(4-chlorophenyl)propyl]-1,6-diethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-cyclobutyl-1-ethyl-N-(phenylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-cyclobutyl-1-ethyl-N-{[4-(methyloxy)phenyl]methyl}-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-(cyclopropylmethyl)-N-[(3,4-dimethylphenyl)methyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-cyclobutyl-N-(2,3-dihydro-1H-inden-2-yl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[(4-chloro-2-methylphenyl)methyl]-6-cyclobutyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;

N-[1-(4-chlorophenyl)ethyl]-6-cyclobutyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[1-(4-chlorophenyl)propyl]-6-cyclobutyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-(cyclopropylmethyl)-1-ethyl-N-(phenylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-(cyclopropylmethyl)-N-[(3,4-dimethylphenyl)methyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-(cyclopropylmethyl)-N-(2,3-dihydro-1H-inden-2-yl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[1-(4-chlorophenyl)ethyl]-6-(cyclopropylmethyl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-cyclopentyl-1-ethyl-N-(phenylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide; or
6-cyclopentyl-N-(2,3-dihydro-1H-inden-2-yl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide.

or a salt thereof, e.g. a pharmaceutically acceptable salt thereof.

The structures of these specific compounds are given in Examples 1 to 29 hereinafter.

Alternatively, it is particularly preferred that the compound of formula (I) or the salt thereof is one of Examples 1 to 29, as a compound or a salt thereof, e.g. a pharmaceutically acceptable salt thereof. The structures of these specific compounds are given in Examples 1 to 29 hereinafter, and their names are given in the Examples section.

In a further aspect the invention provides a compound of formula (I) or a salt thereof selected from the group consisting of:

N-[(4-chloro-2-methylphenyl)methyl]-6-cyclopropyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-cyclopropyl-1-ethyl-N-(phenylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-cyclopropyl-1-ethyl-N-{[4-(methyloxy)phenyl]methyl}-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
6-cyclopropyl-N-[(3,4-dimethylphenyl)methyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
N-[1-(4-chlorophenyl)ethyl]-6-cyclopropyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide; or
N-[1-(4-chlorophenyl)propyl]-6-cyclopropyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;

or a salt thereof, e.g. a pharmaceutically acceptable salt thereof.

Because of their potential use in medicine, the salts of the compounds of formula (I) are preferably pharmaceutically acceptable. Suitable pharmaceutically acceptable salts can include acid or base addition salts.

A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic, formic, acetic, propionic, fumaric, citric, tartaric, lactic, benzoic, salicylic, glutamaic, aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic, or hexanoic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can comprise or be for example a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, formate, acetate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2- naphthalenesulfonate) or hexanoate salt.

A pharmaceutically acceptable base addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic base (e.g. triethylamine, ethanolamine, triethanolamine, choline, arginine, lysine or histidine), optionally in a suitable solvent such as an organic solvent, to give the base addition salt which is usually isolated for example by crystallisation and filtration.

Other suitable pharmaceutically acceptable salts include pharmaceutically acceptable metal salts, for example pharmaceutically acceptable alkali-metal or alkaline-earth-metal salts such as sodium, potassium, calcium or magnesium salts; in particular pharmaceutically acceptable metal salts of one or more carboxylic acid moieties that may be present in the the compound of formula (I).

Other non-pharmaceutically acceptable salts, eg. oxalates, may be used, for example in the isolation of compounds of the invention, and are included within the scope of this invention.

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of formula (I).

Also included within the scope of the invention are all solvates, hydrates and complexes of compounds and salts of the invention.

Certain groups, substituents, compounds or salts included in the present invention may be present as isomers. The present invention includes within its scope all such isomers, including racemates, enantiomers and mixtures thereof.

In the compounds or salts, pharmaceutical compositions, uses, methods of treatment/prophylaxis, methods of preparing, etc. according to the present invention, where a defined isomeric configuration e.g. stereochemical configuration is described or claimed, the invention includes a mixture comprising (a) a major component of the

compound or salt which is in the described or claimed configuration, together with (b) one or more minor components of the compound or salt which is/are not in the described or claimed configuration. Preferably, in such a mixture, the major component of the compound or salt which is in the described or claimed configuration represents 70% or more, or 75% or more, more preferably 85% or more, still more preferably 90% or more, yet more preferably 95% or more, yet more preferably 98% or more, of the total amount of compound or salt present in the mixture on a molarity basis.

The percentage of one isomeric / stereochemical component in a mixture of different isomeric / stereochemical components, and if appropriate enantiomeric and/or diastereomeric excesses, can be measured using techniques known in the art. Such methods include the following:

(1) Measurement using NMR (e.g. ^1H NMR) spectroscopy in the presence of chiral agent. One can measure a nuclear magnetic resonance (NMR) spectrum (preferably a ^1H NMR spectrum, and/or a solution-phase NMR spectrum e.g. in $CDCl_3$ or D6-DMSO solvent) of the compound/salt mixture in the presence of a suitable chiral agent which "splits" the NMR peaks of a given atom in different isomers into different peak positions. The chiral agent can be: i) an optically pure reagent which reacts with the compound/salt e.g. to form a mixture of diastereomers, ii) a chiral solvent, iii) a chiral molecule which forms a transient species (e.g. diastereomeric species) with the compound/salt, or iv) a chiral shift reagent. See e.g. J. March, "Advanced Organic Chemistry", 4th edn., 1992, pages 125-126 and refs. 138-146 cited therein. A chiral shift reagent can be a chiral lanthanide shift reagent such as tris[3-trifluoroacetyl-*d*-camphorato]europium-(III) or others as described in Morrill, "Lanthanide Shift Reagents in Stereochemical Analysis", VCH, New York, 1986. Whatever the chiral agent is that is used, usually, the relative integrals (intensities) for the NMR peaks of a given atom or group in different isomers can provide a measurement of the relative amounts of each isomer present.

(2) Measurement using chiral chromatography, especially on an analytical scale. A suitable chiral column which separates the different isomeric components can be used to effect separation, e.g. using gas or liquid chromatography such as HPLC, and/or e.g. on an analytical scale. The peaks for each isomer can be integrated (area under each peak); and a comparison or ratio of the integrals for the different isomers present can give a measurement of the percentage of each isomeric component present. See for example: "Chiral Chromatography", Separation Science Series Author: T.E. Beesley and R.P.W. Scott, John Wiley & Sons, Ltd., Chichester, UK, 1998, electronic Book ISBN: 0585352690, Book ISBN: 0471974277.

(3) Separation of pre-existing diastereomeric mixtures which are compounds/salts of the invention can be achieved (usually directly, without derivatisation) using separation techniques such as gas or liquid chromatography. Diastereomeric ratios and/or excesses can thereby be derived e.g. from the relative peak areas or relative separated masses.

(4) Conversion with a chiral / optically-active agent and subsequent separation of the resulting isomers, e.g. diastereomers. Conversion can be via derivatisation of a

derivatisable group (e.g. -OH, -NHR) on the compound/salt with an optically-active derivatising group (e.g. optically active acid chloride or acid anhydride); or can be via formation of an acid or base addition salt of the compound by treatment of the compound with an optically-active acid or base, such as + or – di-para-toluoyl tartaric acid. After derivatisation, separation of the resulting isomers e.g. diastereomers, can be using gas or liquid chromatography (usually non-chiral); or (especially with isomeric salts) can be by selective crystallisation of a single isomeric e.g. diastereoisomeric salt. Determination of isomeric ratios and/or excesses can be using chromatography peak areas or measurement of mass of each separated isomer.

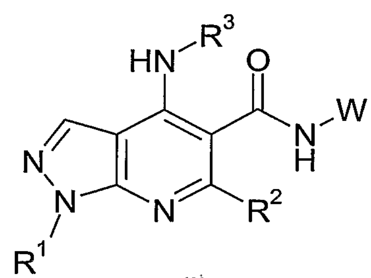
See e.g. J. March, "Advanced Organic Chemistry", 4th edn., 1992, pages 120-121 and 126, and refs. 105-115 and 147-149 cited therein.

(5) Measurement of optical activity [alpha] of mixture and comparison with optical activity of pure isomer $[alpha]_{max}$ if available (e.g. see J. March, "Advanced Organic Chemistry", 4th edn., 1992, page 125 and refs. 138-139 cited therein). This assumes a substantially linear relationship between [alpha] and concentration.

Certain of the groups, e.g. heteroaromatic ring systems, included in compounds of formula (I) or their salts may exist in one or more tautomeric forms. The present invention includes within its scope all such tautomeric forms, including mixtures.

Especially when intended for oral medicinal use, the compound of formula (I) can optionally have a molecular weight of 1000 or less, for example 800 or less, in particular 650 or less or 600 or less. Molecular weight here refers to that of the unsolvated "free base" compound, that is excluding any molecular weight contributed by any addition salts, solvent (e.g. water) molecules, etc.

The following processes can be used to make the compounds of the invention:

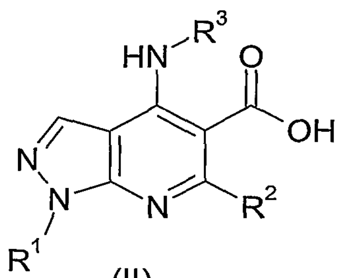


(I)

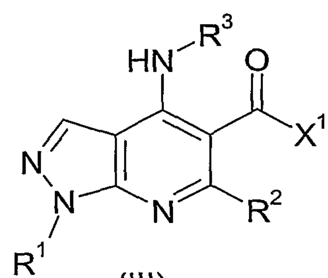
Process A

To form a compound of formula (I) wherein W = $-CR^4R^5Ar$, a carboxylic acid of formula (II) can be converted into an activated compound of formula (III) wherein X^1 = a

leaving group substitutable by an amine (as defined below) and subsequently the activated compound can be reacted with an amine of formula $ArCR^4R^5NH_2$:

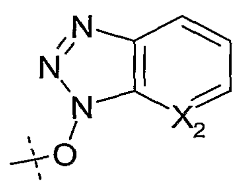


(II)



(III)

For example, the activated compound (the compound of formula (III)) can be the acid chloride. This can be formed from the carboxylic acid (II) e.g. by reaction with thionyl chloride, either in an organic solvent such as chloroform or without solvent. Alternatively, the activated compound (the compound of formula (III)) can be an activated ester wherein the leaving group X^1 is



X_2 = CH or N

The latter activated compound of formula (III) can be formed from the carboxylic acid (II) either:

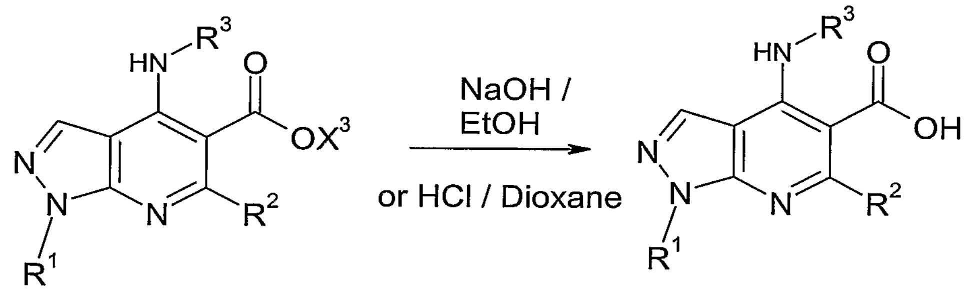
(a) by reaction of the carboxylic acid with a carbodiimide such as EDC, which is 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide and is also 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or a salt thereof e.g. hydrochloride salt, preferably followed by reaction of the resulting product with 1-hydroxybenzotriazole (HOBT); reaction (a) usually being carried out in the presence of a solvent (preferably anhydrous) such as dimethyl formamide (DMF) or acetonitrile and/or preferably under anhydrous conditions and/or usually at room temperature (e.g. about 20 to about 25 °C);

or:

(b) by reaction with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) or O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) ,in the presence of a base such as diisopropylethylamine ($^iPr_2NEt$ = DIPEA), and usually in the presence of a solvent such as dimethyl formamide (DMF) or acetonitrile and/or preferably under anhydrous conditions and/or usually at room temperature (e.g. about 20 to about 25 °C).

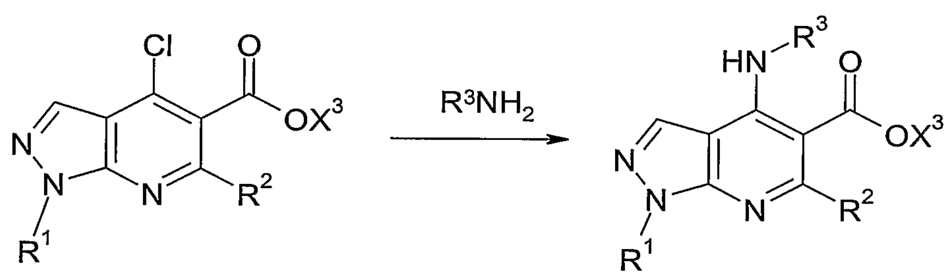
Compounds of formula (II) can be prepared by hydrolysis of an ester of formula (IV). This procedure preferably involves reaction of (IV) with either:

(a) a base such as sodium hydroxide or potassium hydroxide in a solvent e.g. an aqueous solvent such as aqueous ethanol or aqueous dioxane or
(b) an acid such as hydrochloric acid in a solvent e.g. an aqueous solvent such as aqueous dioxane:



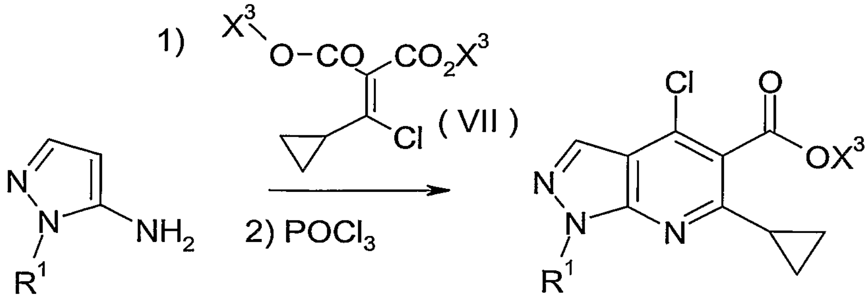
(IV) (II)

Compounds of formula (IV) can be prepared according to a method, for example as described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027, by reaction of a compound of formula (V) with an amine of formula R^3NH_2. The reaction is preferably carried out in the presence of a base such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, dioxane, 1-methyl-2-pyrrolidinone (NMP) or acetonitrile. The reaction may require heating e.g. to ca. 60-180°C, for example ca. 140-160°C:



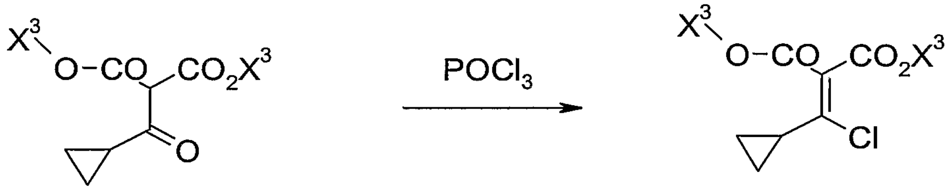
(V) (IV)

Compounds of formula (V) are also described in the above reference and can be prepared by reaction of a compound of formula (VI) with, for example, diethyl[chloro(cyclopropyl)methylene]malonate (VII) (where X^3 = Et) with heating, followed by reaction with phosphorous oxychloride, again with heating:



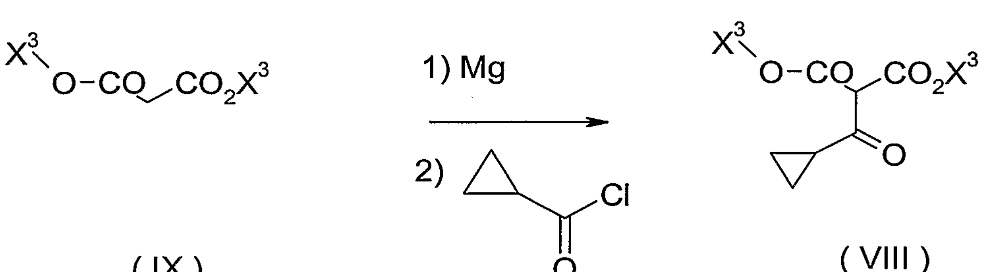
(VI) (V)

Compounds of formula (VII) are also described in the above reference and can be prepared by reaction of a malonate derivative, for example diethyl(cyclopropylcarbonyl)malonate (VIII), with phosphorus oxychloride in the presence of a base such as tributylamine. The reaction may require heating, e.g. to ca 80-130°C, for example ca. 100-120°C:



(VIII) (VII)

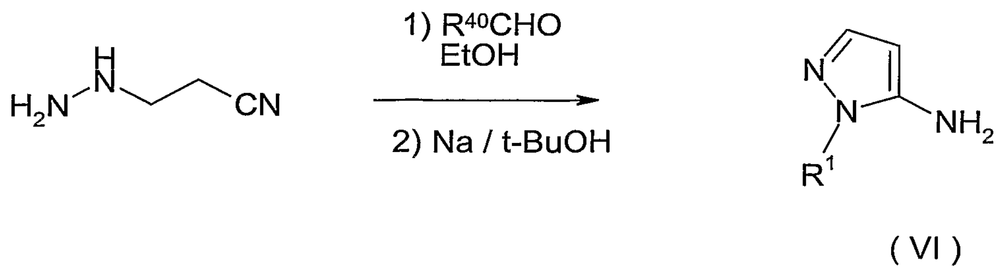
Compounds of formula (VII) are also described in the above reference and can be prepared by reaction of diethyl malonate (IX) with magnesium powder followed by an acid chloride, for example cyclopropylcarbonyl chloride (X).



(IX) (X) (VIII)

Where the desired amino pyrazole of formula (VI) is not commercially available, preparation can be achieved using methods described by Dorgan et. al. in J. Chem. Soc., Perkin Trans. 1, (4), 938-42; 1980, by reaction of cyanoethylhydrazine with a suitable aldehyde of formula $R^{40}CHO$ in a solvent such as ethanol, with heating, followed by reduction with, for example sodium in a solvent such as t-butanol. R^{40} should be chosen

so as to contain one less carbon atom than R^1, for example R^{40} = methyl will afford R^1 = ethyl.



In an alternative embodiment of Process A, the 4-chloro substituent in the compound of formula (V) can be replaced by another halogen atom, such as a bromine atom, or by another suitable leaving group which is displaceable by an amine of formula R^3NH_2. The leaving group can, for example, be an alkoxy group $-OR^{35}$ such as $-OC_{1-4}$alkyl (in particular –OEt) or a group $-O-S(O)_2-R^{37}$, wherein R^{37} is C_{1-8}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl such as methyl), C_{1-6}fluoroalkyl (e.g. C_{1-4}fluoroalkyl or C_{1-2}fluoroalkyl such as CF_3 or C_4F_9), or phenyl wherein the phenyl is optionally substituted by one or two of independently C_{1-2}alkyl, halogen or C_{1-2}alkoxy (such as phenyl or 4-methyl-phenyl). The reaction may be carried out with or without solvent and may require heating.

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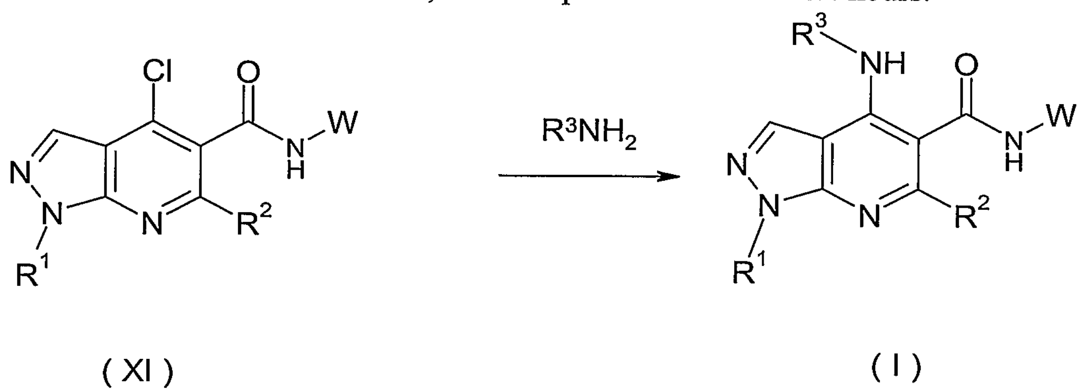
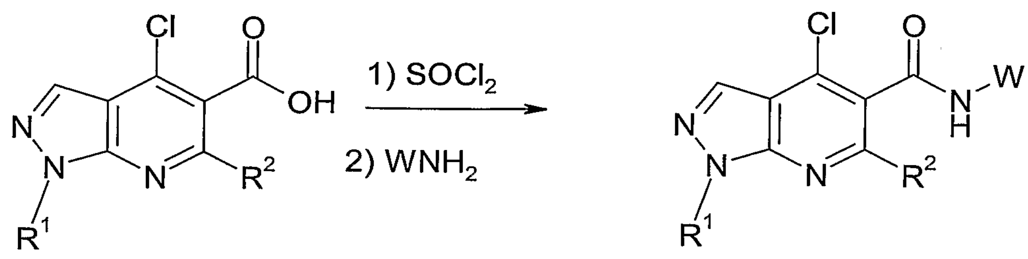
Process B

Compounds of formula (I) can be prepared by reaction of a compound of formula (XI) with an amine of formula R^3NH_2. The reaction is preferably carried out in the presence of a base, such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, THF, dioxane or acetonitrile. The reaction may require heating, e.g. to ca. 60-100 °C or ca. 80-90 °C, for example for 8-48 or 12-24 hours:



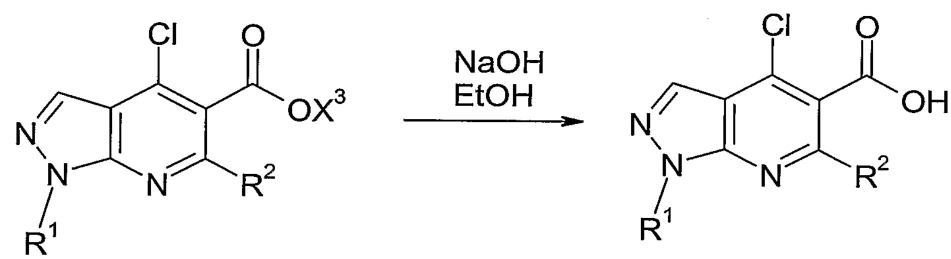
Compounds of formula (XI) can be prepared in a two step procedure as described by Bare et. al. in *J. Med. Chem.* 1989, 32, 2561-2573. This process involves, first, reaction of a compound of formula (XII) with thionyl chloride (or another agent suitable for forming

an acid chloride from a carboxylic acid), either in an organic solvent such as chloroform or THF, or as a neat solution. This reaction may require heating and the thus-formed intermediate may or may not be isolated. Step two involves reaction with an amine of formula WNH_2, in an organic solvent such as THF or chloroform and may also involve the use of a base such as triethylamine or diisopropylethylamine:



(XII) (XI)

Compounds of formula (XII) can be prepared by hydrolysis of an ester of formula (V) according to the method described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027. This procedure preferably involves reaction with a base such as sodium hydroxide or potassium hydroxide in a solvent e.g. an aqueous solvent such as aqueous ethanol or aqueous dioxane:

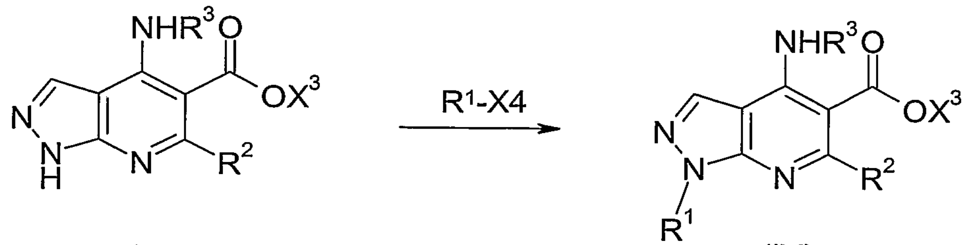


(V) (XII)

In an alternative embodiment of Process B, the 4-chloro substituent in the compound of formula (IV) can be replaced by another halogen atom, such as a bromine atom.

Process C

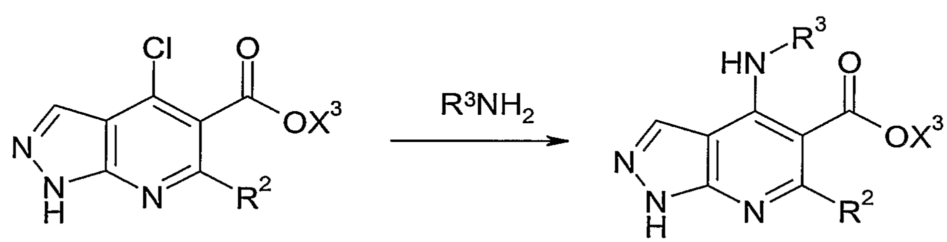
Compounds of formula (IV) can be prepared by reaction of a compound of formula (XIII) with an alkylating agent of formula R^1-X^4, where X^4 is a leaving group displaceable by the 1-position pyrazolopyridine nitrogen atom of the compound of formula (XIII):



(XIII) (IV)

A suitable alkylating agent of formula R^1-X^4 can be used. For example, X^4 can be a halogen atom such as a chlorine atom or more preferably a bromine or iodine atom, or X^3 can be –O-S(O)$_2$-R^{36} wherein R^{36} is C_{1-8}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl such as methyl), C_{1-6}fluoroalkyl (e.g. C_{1-4}fluoroalkyl or C_{1-2}fluoroalkyl such as CF_3 or C_4F_9), or phenyl wherein the phenyl is optionally substituted by one or two of independently C_{1-2}alkyl, halogen or C_{1-2}alkoxy (such as phenyl or 4-methyl-phenyl). The reaction is preferably carried out in the presence of a base; the base can for example comprise or be potassium carbonate, sodium carbonate, sodium hydride, potassium hydride, or a basic resin or polymer such as polymer-bound 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine. The reaction is preferably carried out in the presence of a solvent, e.g. an organic solvent such as DMF; the solvent is preferably anhydrous.

Compounds of formula (XIII) can be prepared, using a method analogous to that used for the preparation of compounds (IV), by reaction of a compound of formula (V) (R^1 = H) with an amine of formula R^3NH_2. The reaction is preferably carried out in the presence of a base such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, dioxane or acetonitrile. The reaction may require heating e.g. to ca. 60-100°C, for example ca. 80-90°C:



(V) (XIII)

Process D: *Conversion of one compound of formula (I)-(IV) or salt thereof into another compound of formula (I)-(IV) or salt thereof*

One compound of formula (I)-(IV) or salt thereof can be converted into another compound of formula (I)-(IV) or salt thereof. This conversion preferably comprises or is one or more of the following processes D1 to D7:

D1. Conversion of a ketone into the corresponding oxime.

D2. An oxidation process. For example, the oxidation process can comprise or be oxidation of an alcohol to a ketone (e.g. using Jones reagent) or oxidation of an alcohol or a ketone to a carboxylic acid.

D3. A reduction process, for example reduction of a ketone or a carboxylic acid to an alcohol.

D4. Alkylation, for example alkylation of an amine or of a hydroxy group.

D5. Hydrolysis, e.g. hydrolysis of an ester to the corresponding carboxylic acid or salt thereof.

D6. Deprotection, e.g. deprotection (e.g. deacylation or t-butyloxycarbonyl (BOC) removal) of an amine group.

D7. Formation of an ester or amide, for example from the corresponding carboxylic acid.

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance in a mammal such as a human. The compound or salt can be for use in the treatment and/or prophylaxis of any of the diseases / conditions described herein (e.g. for use in the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal) and/or for use as a phosphodiesterase inhibitor e.g. for use as a phosphodiesterase 4 (PDE4) inhibitor. "Therapy" may include treatment and/or prophylaxis.

Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament (e.g. pharmaceutical composition) for the treatment and/or prophylaxis of any of the diseases / conditions described herein in a mammal such as a human, e.g. for the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human.

Also provided is a method of treatment and/or prophylaxis of any of the diseases / conditions described herein in a mammal (e.g. human) in need thereof, e.g. a method of treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal (e.g. human) in need thereof, which method comprises administering to the mammal (e.g. human) a therapeutically effective amount of a compound of formula (I) as herein defined or a pharmaceutically acceptable salt thereof.

Phosphodiesterase 4 inhibitors are thought to be useful in the treatment and/or prophylaxis of a variety of diseases / conditions, especially inflammatory and/or allergic diseases, in mammals such as humans, for example: asthma, chronic obstructive pulmonary disease (COPD) (e.g. chronic bronchitis and/or emphysema), atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, adult respiratory distress syndrome, multiple sclerosis, cognitive impairment (e.g. in a neurological disorder such as Alzheimer's disease), depression, or pain. Ulcerative colitis and/or Crohn's disease are collectively often referred to as inflammatory bowel disease.

In the treatment and/or prophylaxis, the inflammatory and/or allergic disease is preferably chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis or allergic rhinitis in a mammal (e.g. human). More preferably, the treatment and/or prophylaxis is of COPD or asthma in a mammal (e.g. human).

PDE4 inhibitors are thought to be effective in the treatment of asthma (e.g. see M.A.Giembycz, *Drugs*, Feb. 2000, 59(2), 193-212; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14), 1255-1296; A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; and references cited in the aforementioned publications).

PDE4 inhibitors are thought to be effective in the treatment of COPD. For example, see S.L. Wolda, *Emerging Drugs*, 2000, 5(3), 309-319; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14), 1255-1296; A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; and references cited in the aforementioned publications; and G. Krishna et al., *Expert Opinion on Investigational Drugs*, 2004, 13(3), 255-267 (see especially pp. 259-261 and refs. 102-111 and 201 therein). COPD is often characterised by the presence of airflow obstruction due to chronic bronchitis and/or emphysema (e.g., see S.L. Wolda, *Emerging Drugs*, 2000, 5(3), 309-319).

PDE4 inhibitors are thought to be effective in the treatment of allergic rhinitis (e.g. see B.M. Schmidt et al., *J. Allergy & Clinical Immunology*, 108(4), 2001, 530-536).

PDE4 inhibitors are thought to be effective in the treatment of rheumatoid arthritis and multiple sclerosis (e.g. see H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002,

8(14), 1255-1296; and A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; and references cited in these publications). See e.g. A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473 and references cited therein for atopic dermatitis use.

PDE4 inhibitors have been suggested as having analgesic properties and thus being effective in the treatment of pain (A.Kumar et al., *Indian J. Exp. Biol.*, 2000, 38(1), 26-30).

In the invention, the treatment and/or prophylaxis can be of cognitive impairment e.g. cognitive impairment in a neurological disorder such as Alzheimer's disease. For example, the treatment and/or prophylaxis can comprise cognitive enhancement e.g. in a neurological disorder. See for example: H.T.Zhang et al. in: *Psychopharmacology*, June 2000, 150(3), 311-316 and *Neuropsychopharmacology*, 2000, 23(2), 198-204; and T. Egawa et al., *Japanese J. Pharmacol.*, 1997, 75(3), 275-81.

PDE4 inhibitors such as rolipram have been suggested as having antidepressant properties (e.g. J. Zhu et al., *CNS Drug Reviews*, 2001, 7(4), 387-398; O'Donnell, *Expert Opinion on Investigational Drugs*, 2000, 9(3), 621-625; and H.T. Zhang et al., *Neuropsychopharmacology*, October 2002, 27(4), 587-595).

For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition.

The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers and/or excipients.

The pharmaceutical composition can be for use in the treatment and/or prophylaxis of any of the conditions described herein.

The invention also provides a method of preparing a pharmaceutical composition comprising a compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers and/or excipients,

the method comprising mixing the compound or salt with the one or more pharmaceutically acceptable carriers and/or excipients.

The invention also provides a pharmaceutical composition prepared by said method.

The compounds of formula (I) and/or the pharmaceutical composition may be administered, for example, by oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. Accordingly , the pharmaceutical composition is preferably suitable for oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. More preferably, the pharmaceutical composition is suitable for inhaled or oral administration, e.g. to a mammal such as a

human. Inhaled administration involves topical administration to the lung e.g. by aerosol or dry powder composition. Oral administration to a human is most preferred.

A pharmaceutical composition suitable for oral administration can be liquid or solid; for example it can be a syrup, suspension or emulsion, a tablet, a capsule or a lozenge.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable pharmaceutically acceptable liquid carrier(s), for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A pharmaceutical composition suitable for oral administration being a tablet can comprise one or more pharmaceutically acceptable carriers and/or excipients suitable for preparing tablet formulations. The carrier can for example be or include lactose, cellulose (for example microcrystalline cellulose), or mannitol. The tablet can also or instead contain one or more pharmaceutically acceptable excipients, for example a binding agent such as hydroxypropylmethylcellulose or povidone (polyvinylpyrollidone), a lubricant e.g. an alkaline earth metal stearate such as magnesium stearate, and/or a tablet disintegrant such as sodium starch glycollate, croscarmellose sodium, or crospovidone (cross-linked polyvinylpyrollidone). The pharmaceutical composition being a tablet can be prepared by a method comprising the steps of: (i) mixing the compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof, with the one or more pharmaceutically acceptable carriers and/or excipients, (ii) compressing the resulting mixture (which is usually in powder form) into tablets, and (iii) optionally coating the tablet with a tablet film-coating material.

A pharmaceutical composition suitable for oral administration being a capsule can be prepared using encapsulation procedures. For example, pellets or powder containing the active ingredient can be prepared using a suitable pharmaceutically acceptable carrier and then filled into a hard gelatin capsule. Alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutically acceptable carrier, for example an aqueous gum or an oil and the dispersion or suspension then filled into a soft gelatin capsule.

Preferably the composition is in unit dose form such as a tablet or capsule for oral administration, e.g. for oral administration to a human.

A parenteral composition can comprise a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil. Alternatively, the solution can be lyophilised; the lyophilised parenteral pharmaceutical composition can be reconstituted with a suitable solvent just prior to administration.

Compositions for nasal or inhaled administration may conveniently be formulated as aerosols, drops, gels or dry powders.

Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities

in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide, or an organic propellant such as a chlorofluorocarbon (CFC) or hydrofluorocarbon (HFC). Suitable CFC propellants include dichlorodifluoromethane, trichlorofluoromethane and dichlorotetrafluoroethane. Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser.

For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the compound or salt of formula (I) is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronisation. Micronisation usually involves subjecting the compound/salt to collisional and/or abrasional forces in a fast-flowing circular or spiral/vortex-shaped airstream often including a cyclone component. The preferable particle size of the size-reduced (e.g. micronised) compound or salt is defined by a D50 value of about 0.5 to about 10 microns, e.g. about 1 to about 7 microns (e.g. as measured using laser diffraction). For example, it is preferable for the compound or salt of formula (I) to have a particle size defined by: a D10 of about 0.3 to about 3 microns (e.g. about 0.5 to about 2 microns, or about 1 micron), and/or a D50 of about 0.5 to about 10 microns or about 1 to about 7 microns (e.g. about 2 to about 5 microns or about 2 to about 4 microns), and/or a D90 of about 1 to about 30 microns or about 2 to about 20 microns or about 3 to about 15 microns (e.g. about 5 to about 15 microns or about 5 to about 10 microns); for example as measured using laser diffraction.

In particle size measurements, D90, D50 and D10 respectively mean that 90%, 50% and 10% of the material is less than the micron size specified. D50 is the median particle size. DV90, DV50 and DV10 respectively mean that 90%, 50% and 10% by volume of the material is less than the micron size specified. DM90, DM50 and DM10 respectively mean that 90%, 50% and 10% by weight of the material is less than the micron size specified.

Laser diffraction measurement of particle size can use a dry method (wherein a suspension of the compound/salt in an airflow crosses the laser beam) or a wet method [wherein a suspension of the compound/salt in a liquid dispersing medium, such as isooctane or (e.g. if compound is soluble in isooctane) 0.1% Tween 80 in water, crosses the laser beam]. With laser diffraction, particle size is preferably calculated using the Fraunhofer calculation; and/or preferably a Malvern Mastersizer or Sympatec apparatus is used for measurement. For example, particle size measurement and/or analysis by laser

diffraction can use any or all of (preferably all of) the following: a Malvern Mastersizer longbed version, a dispersing medium of 0.1% Tween 80 in water, a stir rate of ca. 1500 rpm, ca. 3 mins sonification prior to final dispersion and analysis, a 300 RF (Reverse Fourier) lens, and/or the Fraunhofer calculation with Malvern software.

For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the pharmaceutical composition is a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose or starch, the compound of formula (I) or salt thereof (preferably in particle-size-reduced form, e.g. in micronised form), and optionally a performance modifier such as L-leucine, mannitol, trehalose and/or magnesium stearate. Preferably, the dry powder inhalable composition comprises a dry powder blend of lactose and the compound of formula (I) or salt thereof. The lactose is preferably lactose hydrate e.g. lactose monohydrate and/or is preferably inhalation-grade and/or fine-grade lactose. Preferably, the particle size of the lactose is defined by 90% or more (by weight or by volume) of the lactose particles being less than 1000 microns (micrometres) (e.g. 10-1000 microns e.g. 30-1000 microns) in diameter, and/or 50% or more of the lactose particles being less than 500 microns (e.g. 10-500 microns) in diameter. More preferably, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 300 microns (e.g. 10-300 microns e.g. 50-300 microns) in diameter, and/or 50% or more of the lactose particles being less than 100 microns in diameter. Optionally, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 100-200 microns in diameter, and/or 50% or more of the lactose particles being less than 40-70 microns in diameter. Most importantly, it is preferable that about 3 to about 30% (e.g. about 10%) (by weight or by volume) of the particles are less than 50 microns or less than 20 microns in diameter. For example, without limitation, a suitable inhalation-grade lactose is E9334 lactose (10% fines) (Borculo Domo Ingredients, Hanzeplein 25, 8017 JD Zwolle, Netherlands).

In the dry powder inhalable composition, preferably, the compound of formula (I) or salt thereof is present in about 0.1% to about 70% (e.g. about 1% to about 50%, e.g. about 5% to about 40%, e.g. about 20 to about 30%) by weight of the composition.

An illustrative non-limiting example of a dry powder inhalable composition follows:

Dry Powder Formulation Example - Dry powder Lactose Blend Preparation

Using a size-reduced e.g. micronised form of the compound of formula (I) or salt thereof, the dry powder blend is prepared by mixing the required amount of the compound/salt (e.g. 10 mg, 1% w/w) with inhalation-grade lactose containing 10% fines (e.g. 990 mg, 99% w/w) in a Teflon™ (polytetrafluoroethene) pot in a Mikro-dismembrator ball-mill (but without a ball bearing) at ¾ speed (ca. 2000-2500 rpm) for about 4 hours at each blend concentration. The Mikro-dismembrator (available from B. Braun Biotech International, Schwarzenberger Weg 73-79, D-34212 Melsungen, Germany; www.bbraunbiotech.com) comprises a base with an upwardly-projecting and sidewardly-vibratable arm to which is attached the Teflon ™ pot. The vibration of the arm achieves blending.

Other blends: 10% w/w compound/salt (50 mg) + 90% w/w lactose (450 mg, inhalation-grade lactose containing 10% fines).

Serial dilution of the 1% w/w blend can achieve e.g. 0.1% and 0.3% w/w blends.

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical composition for inhaled administration can be incorporated into a plurality of sealed dose containers (e.g. containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose, e.g. of the dry powder composition, can be administered by inhalation via a device such as the DISKUS TM device, marketed by GlaxoSmithKline. The DISKUS TM inhalation device is usually substantially as described in GB 2,242,134 A. In such device at least one container for the pharmaceutical composition in powder form (the at least one container preferably being a plurality of sealed dose containers mounted longitudinally in a strip or ribbon) is defined between two members peelably secured to one another; the device comprises: means defining an opening station for the said at least one container; means for peeling the members apart at the opening station to open the container; and an outlet, communicating with the opened container, through which a user can inhale the pharmaceutical composition in powder form from the opened container.

Preferably the composition is in unit dose form such as a tablet or capsule for oral administration, e.g. for oral administration to a human.

In the pharmaceutical composition, a or each dosage unit for oral or parenteral administration preferably contains from 0.01 to 3000 mg, more preferably 0.5 to 1000 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. A or each dosage unit for nasal or inhaled administration preferably contains from 0.001 to 50 mg, more preferably 0.01 to 5 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

A pharmaceutically acceptable compound or salt of the invention is preferably administered to a mammal (e.g. human) in a daily oral or parenteral dose of 0.001 mg to 50 mg per kg body weight per day (mg/kg/day), for example 0.01 to 20 mg/kg/day or 0.03 to 10 mg/kg/day or 0.1 to 2 mg/kg/day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

A pharmaceutically acceptable compound or salt of the invention is preferably administered to a mammal (e.g. human) in a daily nasal or inhaled dose of: 0.0001 to 5 mg/kg/day or 0.0001 to 1 mg/kg/day, e.g. 0.001 to 1 mg/kg/day or 0.001 to 0.3 mg/kg/day or 0.001 to 0.1 mg/kg/day or 0.005 to 0.3 mg/kg/day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

The pharmaceutically acceptable compounds or salts of the invention is preferably administered in a daily dose (for an adult patient) of, for example, an oral or parenteral dose of 0.01 mg to 3000 mg per day or 0.5 to 1000 mg per day e.g. 2 to 500 mg per day, or a nasal or inhaled dose of 0.001 to 300 mg per day or 0.001 to 50 mg per day or 0.01 to

30 mg per day or 0.01 to 5 mg per day or 0.02 to 2 mg per day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

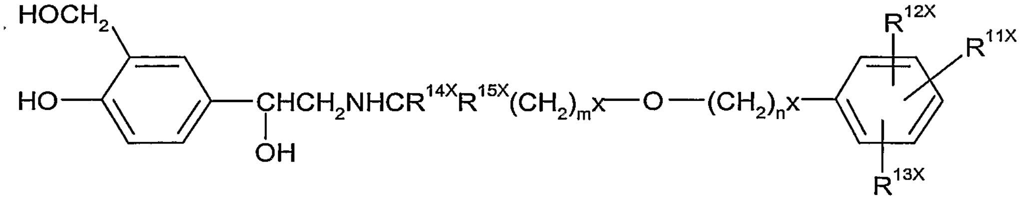
The compounds, salts and/or pharmaceutical compositions according to the invention may also be used in combination with another therapeutically active agent, for example, a β_2 adrenoreceptor agonist, an anti-histamine, an anti-allergic or an anti-inflammatory agent.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with another therapeutically active agent, for example, a β_2-adrenoreceptor agonist, an anti-histamine, an anti-allergic, an anti-inflammatory agent or an antiinfective agent.

Preferably, the β_2-adrenoreceptor agonist is salmeterol (e.g. as racemate or a single enantiomer such as the R-enantiomer), salbutamol, formoterol, salmefamol, fenoterol or terbutaline, or a salt thereof (e.g. pharmaceutically acceptable salt thereof), for example the xinafoate salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. Long-acting β_2-adrenoreceptor agonists are preferred, especially those having a therapeutic effect over a 12-24 hour period such as salmeterol or formoterol. Preferably, the β_2-adrenoreceptor agonist is for inhaled administration, e.g. once per day and/or for simultaneous inhaled administration; and more preferably the β_2-adrenoreceptor agonist is in particle-size-reduced form e.g. as defined herein. Preferably, the β_2-adrenoreceptor agonist combination is for treatment and/or prophylaxis of COPD or asthma. Salmeterol or a pharmaceutically acceptable salt thereof, e.g. salmeterol xinofoate, is preferably administered to humans at an inhaled dose of 25 to 50 micrograms twice per day (measured as the free base). The combination with a β_2-adrenoreceptor agonist can be as described in WO 00/12078.

Preferred long acting β_2-adrenoreceptor agonists include those described in WO 02/066422A, WO 03/024439, WO 02/070490 and WO 02/076933.

Especially preferred long-acting β_2-adrenoreceptor agonists include compounds of formula(XX) (described in WO 02/066422):



(XX)

or a salt or solvate thereof, wherein in formula (XX):
m^X is an integer of from 2 to 8;
n^X is an integer of from 3 to 11,

with the proviso that $m^X + n^X$ is 5 to 19,
R^{11X} is $-XSO_2NR^{16X}R^{17X}$ wherein X is $-(CH_2)_{p^X}$- or C_{2-6} alkenylene;
R^{16X} and R^{17X} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $C(O)NR^{18X}R^{19X}$, phenyl, and phenyl (C_{1-4}alkyl)-,
or R^{16X} and R^{17X}, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring, and R^{16X} and R^{17X} are each optionally substituted by one or two groups selected from halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, hydroxy-substituted C_{1-6}alkoxy, $-CO_2R^{18X}$, $-SO_2NR^{18X}R^{19X}$, $-CONR^{18X}R^{19X}$, $-NR^{18X}C(O)R^{19X}$, or a 5-, 6- or 7-membered heterocylic ring;
R^{18X} and R^{19X} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, and phenyl (C_{1-4}alkyl)-; and
p^X is an integer of from 0 to 6, preferably from 0 to 4;
R^{12X} and R^{13X} are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, phenyl, and C_{1-6}haloalkyl; and
R^{14X} and R^{15X} are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^{14X} and R^{15X} is not more than 4.

Preferred β_2-adrenoreceptor agonists disclosed in WO 02/066422 include:
3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl}amino)hexyl]oxy}butyl)benzenesulfonamide and
3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl}-amino)heptyl]oxy}propyl)benzenesulfonamide.

A preferred β_2-adrenoreceptor agonist disclosed in WO 03/024439 is:
4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol.

A combination of a compound of formula (I) or salt together with an anti-histamine is preferably for oral administration (e.g. as a combined composition such as a combined tablet), and can be for treatment and/or prophylaxis of allergic rhinitis. Examples of anti-histamines include methapyrilene, or H1 antagonists such as cetirizine, loratadine (e.g. Clarityn TM), desloratadine (e.g. Clarinex TM) or fexofenadine (e.g. Allegra TM).

The invention also provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an anticholinergic compound, e.g. a muscarinic (M) receptor antagonist in particular an M_1, M_2, M_1/M_2, or M_3 receptor antagonist, more preferably a M_3 receptor antagonist, still more preferably a M_3 receptor antagonist which selectively antagonises (e.g. antagonises 10 times or more strongly) the M_3 receptor over the M_1 and/or M_2 receptor. For combinations of anticholinergic compounds / muscarinic (M) receptor antagonist with PDE4 inhibitors, see for example WO 03/011274 A2 and WO 02/069945 A2 / US 2002/0193393 A1 and US 2002/052312 A1, and some or all of these publications give examples of

anticholinergic compounds / muscarinic (M) receptor antagonists which may be used with the compounds of formula (I) or salts, and/or suitable pharmaceutical compositions. For example, the muscarinic receptor antagonist can comprise or be an ipratropium salt (e.g. ipratropium bromide), an oxitropium salt (e.g. oxitropium bromide), or more preferably a tiotropium salt (e.g. tiotropium bromide); see e.g. EP 418 716 A1 for tiotropium.

The anticholinergic compound or muscarinic (M) receptor antagonist, e.g. M_3 receptor antagonist, is preferably for inhaled administration, more preferably in particle-size-reduced form e.g. as defined herein. More preferably, both the muscarinic (M) receptor antagonist and the compound of formula (I) or the pharmaceutically acceptable salt thereof are for inhaled administration. Preferably, the anticholinergic compound or muscarinic receptor antagonist and the compound of formula (I) or salt are for simultaneous administration. The muscarinic receptor antagonist combination is preferably for treatment and/or prophylaxis of COPD.

Other suitable combinations include, for example, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with another anti-inflammatory agent such as an anti-inflammatory corticosteroid; or a non-steroidal anti-inflammatory drug (NSAID) such as a leukotriene antagonist (e.g. montelukast), an iNOS inhibitor, a tryptase inhibitor, a elastase inhibitor, a beta-2 integrin antagonist, a adenosine 2a agonist, a CCR3 antagonist, or a 5-lipoxogenase inhibitor; or an antiinfective agent (e.g. an antibiotic or an antiviral). An iNOS inhibitor is preferably for oral administration. Suitable iNOS inhibitors (inducible nitric oxide synthase inhibitors) include those disclosed in WO 93/13055, WO 98/30537, WO 02/50021, WO 95/34534 and WO 99/62875. Suitable CCR3 inhibitors include those disclosed in WO 02/26722.

In a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an anti-inflammatory corticosteroid (which is preferably for treatment and/or prophylaxis of asthma, COPD or allergic rhinitis), then preferably the anti-inflammatory corticosteroid is fluticasone, fluticasone propionate (e.g. see US patent 4,335,121), beclomethasone, beclomethasone 17-propionate ester, beclomethasone 17,21-dipropionate ester, dexamethasone or an ester thereof, mometasone or an ester thereof, ciclesonide, budesonide, flunisolide, or a compound as described in WO 02/12266 A1 (e.g. as claimed in any of claims 1 to 22 therein), or a pharmaceutically acceptable salt of any of the above. If the anti-inflammatory corticosteroid is a compound as described in WO 02/12266 A1, then preferably it is Example 1 therein {which is 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester} or Example 41 therein {which is 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester}, or a pharmaceutically acceptable salt thereof. The anti-inflammatory corticosteroid is preferably for intranasal or inhaled administration. Fluticasone propionate is preferred

and is preferably for inhaled administration to a human either (a) at a dose of 250 micrograms once per day or (b) at a dose of 50 to 250 micrograms twice per day.

Also provided is a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with β_2-adrenoreceptor agonist and an anti-inflammatory corticosteroid, for example as described in WO 03/030939 A1. Preferably this combination is for treatment and/or prophylaxis of asthma, COPD or allergic rhinitis. The β_2-adrenoreceptor agonist and/or the anti-inflammatory corticosteroid can be as described above and/or as described in WO 03/030939 A1. Most preferably, in this "triple" combination, the β_2-adrenoreceptor agonist is salmeterol or a pharmaceutically acceptable salt thereof (e.g. salmeterol xinafoate) and the anti-inflammatory corticosteroid is fluticasone propionate.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus a pharmaceutical composition comprising a combination as defined above together with one or more pharmaceutically acceptable carriers and/or excipients represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical composition.

In one embodiment, the combination as defined herein can be for simultaneous inhaled administration and is disposed in a combination inhalation device. Such a combination inhalation device is another aspect of the invention. Such a combination inhalation device can comprise a combined pharmaceutical composition for simultaneous inhaled administration (e.g. dry powder composition), the composition comprising all the individual compounds of the combination, and the composition being incorporated into a plurality of sealed dose containers mounted longitudinally in a strip or ribbon inside the inhalation device, the containers being rupturable or peel-openable on demand; for example such inhalation device can be substantially as described in GB 2,242,134 A (DISKUS ™) and/or as described above. Alternatively, the combination inhalation device can be such that the individual compounds of the combination are administrable simultaneously but are stored separately (or wholly or partly stored separately for triple combinations), e.g. in separate pharmaceutical compositions, for example as described in PCT/EP03/00598 filed on 22 January 2003, published as WO 03/061743 (e.g. as described in the claims thereof e.g. claim 1).

The invention also provides a method of preparing a combination as defined herein, the method comprising either

(a) preparing a separate pharmaceutical composition for administration of the individual compounds of the combination either sequentially or simultaneously, or

(b) preparing a combined pharmaceutical composition for administration of the individual compounds of the combination simultaneously,

wherein the pharmaceutical composition comprises the combination together with one or more pharmaceutically acceptable carriers and/or excipients.

The invention also provides a combination as defined herein, prepared by a method as defined herein.

BIOLOGICAL TEST METHODS

PDE 3, PDE 4B, PDE 4D, PDE 5, PDE 6 Primary assay methods

The activity of the compounds can be measured in the assay methods shown below. Preferred compounds of the invention are selective PDE4 inhibitors, i.e. they inhibit PDE4 (e.g. PDE4B and/or PDE4D, preferably PDE4B) more strongly than they inhibit PDE3 and/or more strongly than they inhibit PDE5 and/or more strongly than they inhibit PDE6.

PDE enzyme sources and literature references

Human recombinant PDE4B, in particular the 2B splice variant thereof (HSPDE4B2B), is disclosed in WO 94/20079 and also M.M. McLaughlin et al., "A low *K*m, rolipram-sensitive, cAMP-specific phosphodiesterase from human brain: cloning and expression of cDNA, biochemical characterisation of recombinant protein, and tissue distribution of mRNA", *J. Biol. Chem.*, 1993, **268**, 6470-6476. For example, in Example 1 of WO 94/20079, human recombinant PDE4B is described as being expressed in the PDE-deficient yeast *Saccharomyces cerevisiae* strain GL62, e.g. after induction by addition of 150 uM $CuSO_4$, and 100,000 x *g* supernatant fractions of yeast cell lysates are described for use in the harvesting of PDE4B enzyme.

Human recombinant PDE4D (HSPDE4D3A) is disclosed in P. A. Baecker et al., "Isolation of a cDNA encoding a human rolipram-sensitive cyclic AMP phoshodiesterase (PDE IV_D)", *Gene*, 1994, **138**, 253-256.

Human recombinant PDE5 is disclosed in K. Loughney et al., "Isolation and characterisation of cDNAs encoding PDE5A, a human cGMP-binding, cGMP-specific 3',5'-cyclic nucleotide phosphodiesterase", *Gene*, 1998, **216**, 139-147.

PDE3 can be purified from bovine aorta, e.g. as described by H. Coste and P. Grondin, "Characterisation of a novel potent and specific inhibitor of type V phosphodiesterase", *Biochem. Pharmacol.*, 1995, **50**, 1577-1585.

PDE6 can be purified from bovine retina, e.g. as described by: P. Catty and P. Deterre, "Activation and solubilization of the retinal cGMP-specific phosphodiesterase by limited proteolysis", *Eur. J. Biochem.*, 1991, **199**, 263-269; A. Tar et al. "Purification of bovine retinal cGMP phosphodiesterase", *Methods in Enzymology*, 1994, **238**, 3-12; and/or D. Srivastava et al. "Effects of magnesium on cyclic GMP hydrolysis by the bovine retinal rod cyclic GMP phosphodiesterase", *Biochem. J.*, 1995, **308**, 653-658.

Inhibition of PDE 3, PDE 4B, PDE 4D, PDE 5 or PDE 6 activity: radioactive Scintillation Proximity Assay (SPA)

The ability of compounds to inhibit catalytic activity at PDE4B or 4D (human recombinant), PDE3 (from bovine aorta), PDE5 (human recombinant) or PDE6 (from bovine retina) is determined by Scintillation Proximity Assay (SPA) in 96-well format. Test compounds (as a solution in DMSO, preferably about 2 microlitre (ul) volume of DMSO solution) are preincubated at ambient temperature (room temperature, e.g. 19-23°C) in Wallac Isoplates (code 1450-514) with PDE enzyme in 50mM Tris-HCl buffer pH 7.5 , 8.3mM $MgCl_2$, 1.7mM EGTA, 0.05% (w/v) bovine serum albumin for 10-30 minutes (usually 30 minutes). The enzyme concentration is adjusted so that no more than 20% hydrolysis of the substrate defined below occurs in control wells without compound, during the incubation. For the PDE3, PDE4B and PDE4D assays, [5',8-^{3}H]Adenosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech, code TRK.559; or Amersham Biosciences UK Ltd, Pollards Wood, Chalfont St Giles, Buckinghamshire HP8 4SP, UK) is added to give 0.05uCi per well and ~ 10nM final concentration. For the PDE5 and PDE6 assays, [8-^{3}H]Guanosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech, code TRK.392) is added to give 0.05uCi per well and ~ 36nM final concentration. Plates containing assay mixture, preferably approx. 100 ul volume of assay mixture, are mixed on an orbital shaker for 5 minutes and incubated at ambient temperature for 1 hour. Phosphodiesterase SPA beads (Amersham Pharmacia Biotech, code RPNQ 0150) are added (~1mg per well) to terminate the assay. Plates are sealed and shaken and allowed to stand at ambient temperature for 35 minutes to 1hour (preferably 35 minutes) to allow the beads to settle. Bound radioactive product is measured using a WALLAC TRILUX 1450 Microbeta scintillation counter. For inhibition curves, 10 concentrations (1.5nM - 30uM) of each compound are assayed. Curves are analysed using ActivityBase and XLfit (ID Business Solutions Limited, 2 Ocean Court, Surrey Research Park, Guildford, Surrey GU2 7QB, United Kingdom) Results are expressed as pIC_{50} values.

In an alternative to the above radioactive SPA assay, PDE4B or PDE4D inhibition can be measured in the following Fluorescence Polarisation (FP) assay:

Inhibition of PDE4B or PDE4D activity: Fluorescence Polarisation (FP) assay

The ability of compounds to inhibit catalytic activity at PDE4B (human recombinant) or PDE4D (human recombinant) is determined by IMAP Fluorescence Polarisation (FP) assay (IMAP Explorer kit, available from Molecular Devices Corporation, Sunnydale, CA, USA; Molecular Devices code: R8062) in 384-well format. The IMAP FP assay is able to measure PDE activity in an homogenous, non-radioactive assay format. The FP assay uses the ability of immobilised trivalent metal cations, coated onto nanoparticles (tiny beads), to bind the phosphate group of Fl-AMP that is produced on the hydrolysis of fluorescein-labelled (Fl) cyclic adenosine mono-phosphate (Fl-cAMP) to the non-cyclic Fl-AMP form. Fl-cAMP does not bind. Binding of Fl-AMP product to the beads (coated with the immobilised trivalent cations) slows the rotation of

the bound Fl-AMP and leads to an increase in the fluorescence polarisation ratio of parallel to perpendicular light. Inhibition of the PDE reduces/inhibits this signal increase.

Test compounds (small volume, e.g. ca. 0.5 to 1 ul, preferably ca. 0.5 ul, of solution in DMSO) are preincubated at ambient temperature (room temperature, e.g. 19-23°C) in black 384-well microtitre plates (supplier: NUNC, code 262260) with PDE enzyme in 10mM Tris-HCl buffer pH 7.2, 10mM $MgCl_2$, 0.1% (w/v) bovine serum albumin, and 0.05% NaN_3 for 10-30 minutes. The enzyme level is set by experimentation so that reaction is linear throughout the incubation. Fluorescein adenosine 3',5'-cyclic phosphate (from Molecular Devices Corporation, Molecular Devices code: R7091) is added to give about 40nM final concentration (final assay volume usually ca. 20-40 ul, preferably ca. 20 ul). Plates are mixed on an orbital shaker for 10 seconds and incubated at ambient temperature for 40 minutes. IMAP binding reagent (as described above, from Molecular Devices Corporation, Molecular Devices code: R7207) is added (60ul of a 1 in 400 dilution in binding buffer of the kit stock solution) to terminate the assay. Plates are allowed to stand at ambient temperature for 1 hour. The Fluorescence Polarisation (FP) ratio of parallel to perpendicular light is measured using an Analyst™ plate reader (from Molecular Devices Corporation). For inhibition curves, 10 concentrations (1.5nM - 30uM) of each compound are assayed. Curves are analysed using ActivityBase and XLfit (ID Business Solutions Limited, 2 Ocean Court, Surrey Research Park, Guildford, Surrey GU2 7QB, United Kingdom). Results are expressed as pIC_{50} values.

In the FP assay, all reagents are dispensed using Multidrop™ (available from Thermo Labsystems Oy, Ratastie 2, PO Box 100, Vantaa 01620, Finland).

For a given PDE4 inhibitor, the PDE4B (or PDE4D) inhibition values measured using the SPA and FP assays can differ slightly. However, in a regression analysis of 100 test compounds (not necessarily compounds of the invention), the pIC_{50} inhibition values measured using SPA and FP assays have been found generally to agree within 0.5 log units, for PDE4B and PDE4D (linear regression coefficient 0.966 for PDE4B and 0.971 for PDE4D; David R.Mobbs et al., "Comparison of the IMAP Fluorescence Polarisation Assay with the Scintillation Proximity Assay for Phosphodiesterase Activity", poster presented at 2003 Molecular Devices UK & Europe User Meeting, 2nd October 2003, Down Hall, Harlow, Essex, United Kingdom).

Biological Data obtained for some of the Examples (PDE4B inhibitory activity, either as one reading or as an average of ca. 2-6 readings) are as follows, based on current measurements only. In each of the SPA and FP assays, absolute accuracy of measurement is not possible, and the readings given are accurate only up to about ± 0.5 of a log unit, depending on the number of readings made and averaged:

All of the Examples have been tested for PDE4B inhibition using the radioactive SPA assay or the FP assay or in a similar assay. All of the Examples tested have PDE4B inhibitory activities in the range of pIC_{50} = about 7 (± about 0.5) to about 9 (± about 0.5).

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

EXAMPLES

The various aspects of the invention will now be described by reference to the following examples. These examples are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In this section, "Intermediates" represent syntheses of intermediate compounds intended for use in the synthesis of the "Examples".

Abbreviations used herein:

CCl_4	carbon tetrachloride
DCM	dichloromethane
DMF	dimethyl formamide
DIPEA	diisopropylethyl amine ($^iPr_2NEt$)
EtOAc	ethyl acetate
Et_2O	diethyl ether
Et_3N	triethylamine
EtOH	ethanol
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HCl	hydrogen chloride/hydrochloric acid
Na_2SO_4	sodium sulfate
$NaHCO_3$	sodium bicarbonate
NMP	1-methyl-2-pyrrolidinone
$PhCH_3$	toluene
PPA	polyphosphoric acid
HPLC	high pressure liquid chromatography
SPE	solid phase extraction
NMR	nuclear magnetic resonance (in which: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, H = no. of protons)
LCMS	liquid chromatography/mass spectroscopy
TLC	thin layer chromatography
h	hours
T_{RET}	retention time
Room temperature	this is usually in the range of about 20 to about 25 °C.

General Experimental Details

Machine Methods used herein:

LCMS (liquid chromatography/mass spectroscopy)

Waters ZQ mass spectrometer operating in positive ion electrospray mode, mass range 100-1000 amu.
UV wavelength : 215-330nM
Column : 3.3cm x 4.6mm ID, 3μm ABZ+PLUS
Flow Rate : 3ml/min
Injection Volume : 5μl
Solvent A : 95% acetonitrile + 0.05% formic acid
Solvent B : 0.1% formic acid + 10mMolar ammonium acetate
Gradient : 0% A/0.7min, 0-100% A/3.5min, 100% A/1.1min, 100-0% A/0.2min
It should be noted that retention times (T_{RET}) quoted herein may vary slightly (+/-0.1min.) when samples were run on different Waters machines, even though the same type of column and identical flow rates, injection volumes, solvents and gradients were used.

Mass directed autoprep HPLC
The prep column used was a Supelcosil ABZplus (10cm x 2.12cm) (usually 10cm x 2.12cm x 5 μm).
UV wavelength : 200-320nM
Flow : 20ml/min
Injection Volume: 1ml; or more preferably 0.5 ml
Solvent A : 0.1% formic acid
Solvent B : 95% acetonitrile + 5% formic acid; or more usually 99.95% acetonitrile + 0.05% formic acid
Gradient : 100% A/1min, 100-80% A/9min, 80-1% A/3.5min, 1% A/1.4min, 1-100%A/0.1min

Intermediates and Examples

All reagents not detailed in the text below are commercially available from established suppliers such as Sigma-Aldrich. The addresses of the suppliers for some of the starting materials mentioned in the Intermediates and Examples below or the Assays above are as follows:

- Aldrich (catalogue name), Sigma-Aldrich Company Ltd., Dorset, United Kingdom, telephone: +44 1202 733114; Fax: +44 1202 715460; ukcustsv@eurnotes.sial.com; or
- Aldrich (catalogue name), Sigma-Aldrich Corp., P.O. Box 14508, St. Louis, MO 63178-9916, USA; telephone: 314-771-5765; fax: 314-771-5757; custserv@sial.com; or
- Aldrich (catalogue name), Sigma-Aldrich Chemie Gmbh, Munich, Germany; telephone: +49 89 6513 0; Fax: +49 89 6513 1169; deorders@eurnotes.sial.com.
- Bionet Research Ltd; Highfield Industrial Estate, Camelford, Cornwall PL32 9QZ UK
- Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126, USA (CAS 38041-19-9)
- Lancaster Synthesis Ltd., Newgate, White Lund, Morecambe, Lancashire LA3 3DY, United Kingdom

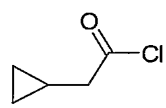
- Matrix Scientific, P.O. Box 25067, Columbia, SC 29224-5067, USA
- Trans World Chemicals, Inc., 14674 Southlawn Lane, Rockville, MD 20850, USA

Table of Intermediates

Intermediate Number	Name
1	Diethyl (cyclopropylcarbonyl)malonate
2	Diethyl (cyclopentylcarbonyl) malonate
3	Diethyl (propylcarbonyl)malonate
4	Diethyl (ethylcarbonyl)malonate
5	Diethyl (cyclobutylcarbonyl)malonate
6	Diethyl (cyclopropylmethylcarbonyl)malonate
7	Diethyl [chloro(cyclopropyl)methylene]malonate
8	Diethyl [chloro(propyl)methylene] malonate
9	Diethyl [chloro(ethyl)methylene] malonate
10	Diethyl [chloro(cyclobutyl)methylene] malonate
11	Diethyl [chloro(cyclopropylmethyl)methylene] malonate
12	Ethyl 4-chloro-6-cyclopropyl-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
13	Ethyl-4-chloro-6-propyl-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
14	Ethyl-4-chloro-6-ethyl-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
15	Ethyl-4-chloro-6-cyclobutyl-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
16	Ethyl-4-chloro-6-cyclopropylmethyl-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
17	Ethyl-4-chloro-6-cyclopentyl-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
18	4-Aminotetrahydropyran
19	Ethyl 6-cyclopropyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
20	Ethyl 6-propyl- 1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
21	Ethyl 6-ethyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
22	Ethyl 6-cyclobutyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
23	Ethyl 6-cyclopropylmethyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
24	Ethyl 6-cyclopentyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate

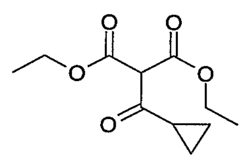
25	6-Cyclopropyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
26	6-propyl- 1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5- carboxylic acid
27	6-Ethyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
28	6-Cyclobutyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5- carboxylic acid
29	6-Cyclopropylmethyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5- carboxylic acid
30	6-Cyclopentyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5- carboxylic acid

Cyclopropylacetyl chloride



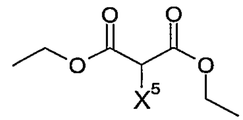
Prepared from cyclopropyl acetic acid according to the procedure outlined in: Bouzoubaa, Mohamed; Leclerc, Gerard; Decker, Nicole; Schwartz, Jean; Andermann, Guy; J.Med.Chem; 1984, 27 (10); 1291-1294.

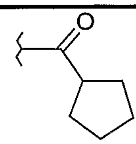
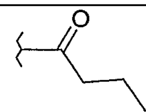
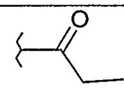
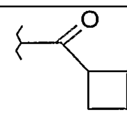
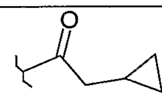
__Intermediate 1__: **Diethyl (cyclopropylcarbonyl)malonate**



A solution of diethyl malonate (6ml) in EtOH (20ml) was added to solid magnesium powder (1g) and CCl_4 (1ml) at such a rate as to maintain a constant reflux. Et_2O (20ml) was added and the mixture was heated under reflux for 2h. The solvents were removed under reduced pressure and the residue was azeotroped with $PhCH_3$ (2x10ml). The solid residue was dissolved in Et_2O (40ml) and the solution was added to a cooled solution of cylopropane carbonyl chloride (3.6ml), maintaining the temperature between 0 and 5°C. The mixture was allowed to warm slowly to room temperature and stirred for 16 hours. The mixture was treated with 5% aqueous sulphuric acid solution (100ml), with stirring. The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (2x75ml), dried over anhydrous Na_2SO_4, filtered and the filtrate evaporated to dryness to leave Intermediate 1 as a colourless oil (7.74g). LCMS showed $MH^+ = 229$; $T_{RET} = 2.79$min.

Similarly prepared from diethyl malonate were the following:

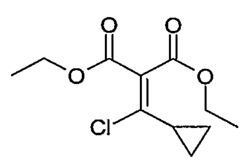


	X^5	MH^+ ion	T_{RET} (min)
Intermediate 2		257	3.2
Intermediate 3		231	3.09
Intermediate 4		217	2.81
Intermediate 5		243	3.07
Intermediate 6		243	3.07

Intermediates 7-11

These intermediates were prepared using a modification of the procedure developed by O.E.O. Hormi and described in *Synthetic Commun; 1986, 16, 997 - 1002.*

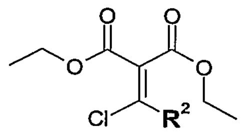
<u>Intermediate 7:</u> Diethyl [chloro(cyclopropyl)methylene]malonate

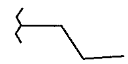
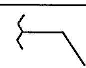
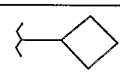
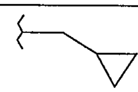


A mixture of Intermediate 1 (1g), phosphorus oxychloride (10ml) and tributylamine (1.1ml) was stirred at 110°C for 5h. The volatile organics were removed under reduced pressure. The mixture was dissolved in Et_2O (20ml) and n-hexane was added until two layers formed. The top layer was collected. More n-hexane was added until two layers formed again. This procedure was repeated once more. The combined Et_2O extracts were washed with dilute aqueous HCl (1M, 2x50ml), dilute aqueous NaOH (1M, 2x50ml) and

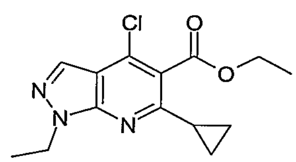
water (2x50ml), dried over anhydrous Na_2SO_4, filtered and evaporated to give Intermediate 7 as a pale yellow oil (0.87g). LCMS showed $MH^+ = 249$; $T_{RET} = 3.49$min.

Similarly prepared from Intermediates 3-6 were the following:



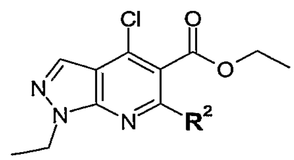
	Precursor	**R^2**	**MH^+ ion**	**T_{RET} (min)**
Intermediate 8	Intermediate 3		249	3.45
Intermediate 9	Intermediate 4		235	3.21
Intermediate 10	Intermediate 5		261	3.44
Intermediate 11	Intermediate 6		261	3.23

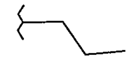
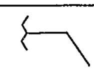
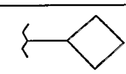
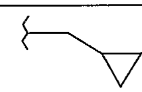
<u>Intermediate 12:</u> Ethyl 4-chloro-6-cyclopropyl-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



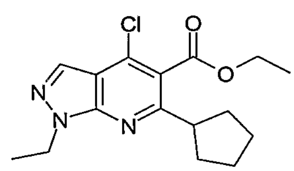
A mixture of intermediate 7 (6.75g), Et_3N (2.88ml) and 5-amino-1-ethyl pyrazole (3.28g) in $PhCH_3$ (40ml) was heated at reflux for 16 hours. The solvent was removed under reduced pressure and the residue was treated with phosphorus oxychloride (50ml). The reaction mixture was heated at 110°C for 16 hours. The phosphorus oxychloride was removed under reduced pressure and the residue was partitioned between EtOAc (50ml) and saturated aqueous $NaHCO_3$ (50ml). The organic layer was collected, dried (Na_2SO_4), filtered and the filtrate was concentrated under reduced pressure. The residue was purified on a 50g SiO_2 SPE cartridge, eluting with 5%EtOAc: 95% cyclohexane, to give Intermediate 12 as a yellow oil (1.53g). LCMS showed $MH^+ = 294$; $T_{RET} = 3.4$min.

Similarly prepared from Intermediates 8-11 were the following:



	Precursor	R^2	MH^+ ion	T_{RET} (min)
Intermediate 13	Intermediate 8		296	3.63
Intermediate 14	Intermediate 9		282	3.4
Intermediate 15	Intermediate 10		308	3.71
Intermediate 16	Intermediate 11		308	3.71

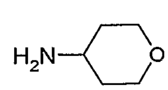
<u>Intermediate 17:</u> Ethyl-4-chloro-6-cyclopentyl-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



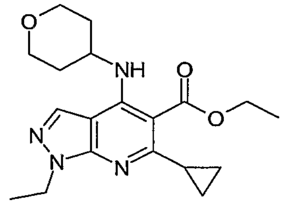
A mixture of Intermediate 2 (1.6g) and 5-amino-1-ethyl pyrazole (0.69g) in PPA (12ml) was heated at 120°C for 3h. The mixture was poured into water (50ml) and extracted with Et_2O (3x75ml). The organic extracts were combined, dried (Na_2SO_4), filtered and the filtrate concentrated to leave a yellow oil. Phosphorus oxychloride (50ml) was added to the oil. The mixture was heated at 110° for 16h. The phosphorus oxychloride was removed and the residue was partitioned between EtOAc (50ml) and saturated aqueous $NaHCO_3$ (25ml). The organic layer was collected, dried (Na_2SO4), filtered and the filtrate was concentrated to leave Intermediate 17 as a tan solid (100mg). LCMS showed MH^+ = 322; T_{RET} = 3.96min.

<u>Intermediate 18:</u> 4-Aminotetrahydropyran

Commercially available from Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126, USA (CAS 38041-19-9)

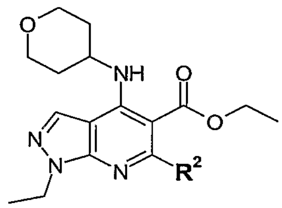


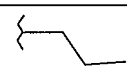
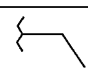
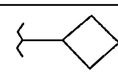
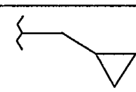
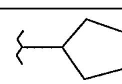
<u>Intermediate 19:</u> Ethyl 6-cyclopropyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



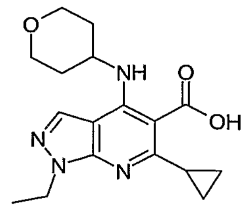
A solution of Intermediate 12 (0.76g), Intermediate 18 (0.36g) and DIPEA (0.65ml) in NMP (8ml) was heated at 150°C for 16h. The mixture was allowed to cool and partitioned between EtOAc (100ml) and water (20ml). The organic layer was collected, dried (Na_2SO_4), filtered and concentrated to give a dark gum. The gum was purified on a 20g SiO_2 SPE cartridge, eluting with 10%EtOAc : 90% Cyclohexane to give Intermediate 18 as a pale yellow solid (0.35g). LCMS showed $MH^+ = 359$; $T_{RET} = 3.43$min.

Similarly prepared from Intermediates 13-17 were the following:



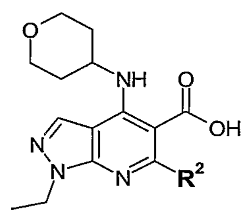
	Precursor	R^2	MH^+ ion	T_{RET} (min)
Intermediate 20	Intermediate 13		361	3.16
Intermediate 21	Intermediate 14		347	3.05
Intermediate 22	Intermediate 15		373	3.57
Intermediate 23	Intermediate 16		373	3.35
Intermediate 24	Intermediate 17		387	3.78

<u>Intermediate 25:</u> 6-Cyclopropyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



A solution of intermediate 19 (0.35g) in EtOH (60ml) was treated with a solution of NaOH (0.75g) in water (20ml) and the reaction mixture was heated at 60°C for 16h. The solvents were removed under reduced pressure, the residue was suspended in water (5ml) and the pH of the solution was adjusted to 3 (1M HCl). The resultant suspension was extracted with EtOAc (2x30ml). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give Intermediate 25 as a white solid (0.30g). LCMS showed $MH^+ = 331$; $T_{RET} = 2.41$min

Similarly prepared from Intermediates 21-25 were the following:



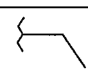
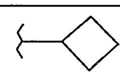
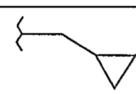
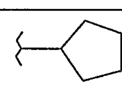
	Precursor	**R^2**	**MH^+ ion**	**T_{RET} (min)**
Intermediate 26	Intermediate 21		333	2.06
Intermediate 27	Intermediate 22		319	1.9
Intermediate 28	Intermediate 23		345	2.61
Intermediate 29	Intermediate 24		345	2.12
Intermediate 30	Intermediate 25		359	2.72

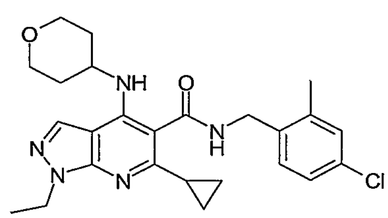
Table of Examples

Example	**Name**

Number	
1	N-[(4-chloro-2-methylphenyl)methyl]-6-cyclopropyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
2	6-cyclopropyl-1-ethyl-N-(phenylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
3	6-cyclopropyl-1-ethyl-N-{[4-(methyloxy)phenyl]methyl}-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4	6-cyclopropyl-N-[(3,4-dimethylphenyl)methyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
5	N-[1-(4-chlorophenyl)ethyl]-6-cyclopropyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
6	N-[1-(4-chlorophenyl)propyl]-6-cyclopropyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
7	1-ethyl-N-(phenylmethyl)-6-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
8	1-ethyl-N-{[4-(methyloxy)phenyl]methyl}-6-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
9	N-[(4-chloro-2-methylphenyl)methyl]-1-ethyl-6-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
10	N-[(3,4-dimethylphenyl)methyl]-1-ethyl-6-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
11	N-(2,3-dihydro-1H-inden-2-yl)-1-ethyl-6-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
12	1,6-diethyl-N-(phenylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
13	1,6-diethyl-N-{[4-(methyloxy)phenyl]methyl}-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
14	N-[(3,4-dimethylphenyl)methyl]-1,6-diethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
15	N-(2,3-dihydro-1H-inden-2-yl)-1,6-diethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
16	N-[1-(4-chlorophenyl)propyl]-1,6-diethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
17	6-cyclobutyl-1-ethyl-N-(phenylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
18	6-cyclobutyl-1-ethyl-N-{[4-(methyloxy)phenyl]methyl}-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
19	6-(cyclopropylmethyl)-N-[(3,4-dimethylphenyl)methyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
20	6-cyclobutyl-N-(2,3-dihydro-1H-inden-2-yl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
21	N-[(4-chloro-2-methylphenyl)methyl]-6-cyclobutyl-1-ethyl-4-(tetrahydro-

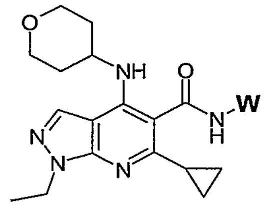
	2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
22	N-[1-(4-chlorophenyl)ethyl]-6-cyclobutyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
23	N-[1-(4-chlorophenyl)propyl]-6-cyclobutyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
24	6-(cyclopropylmethyl)-1-ethyl-N-(phenylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
25	6-(cyclopropylmethyl)-N-[(3,4-dimethylphenyl)methyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
26	6-(cyclopropylmethyl)-N-(2,3-dihydro-1H-inden-2-yl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
27	N-[1-(4-chlorophenyl)ethyl]-6-(cyclopropylmethyl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
28	6-cyclopentyl-1-ethyl-N-(phenylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
29	6-cyclopentyl-N-(2,3-dihydro-1H-inden-2-yl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

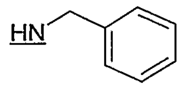
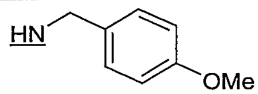
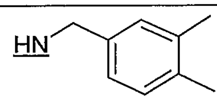
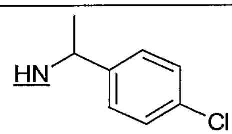
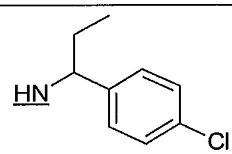
<u>**Example 1:**</u> **N-[(4-chloro-2-methylphenyl)methyl]-6-cyclopropyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



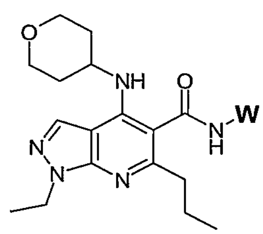
A solution of Intermediate 20 (30mg) in DMF (2ml) was treated with HATU (35mg) and DIPEA (100µL). The solution was allowed to stand at 22°C for 10min. then treated with 2-methyl-4-chloro benzylamine (supplier: Matrix Scientific) (14mg) and allowed to stand at 22°C for 16h. The solvent was evaporated and the residue was partitioned between DCM (5ml) and saturated aqueous $NaHCO_3$ (2ml). The organic phase was collected through a hydrophobic frit and evaporated. The residue was purified by mass directed autoprep. HPLC to give Example 1as a white solid (14.9mg). LCMS showed $MH^+ = 468$; $T_{RET} = 3.45$min.

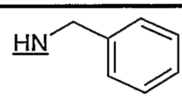
The following Examples 2-6 were prepared from Intermediate 20 and the appropriate amine WNH_2 using a similar procedure to that used for the preparation of Example 1:

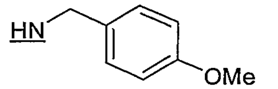
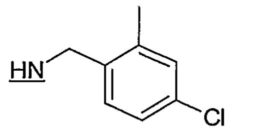
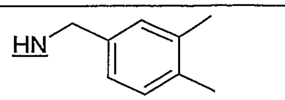
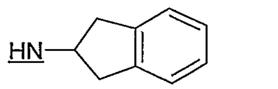


Example No.	NHW	Source of amine reagent WNH_2	MH^+ ion	T_{RET} (min)
2		Aldrich	420	3.02
3		Aldrich	450	2.99
4		Trans World Chemicals	448	3.27
5		Bionet Research	468	3.39
6		J. Pharm. Pharmacol; 1997, 49 (1), 10-15	482	3.51

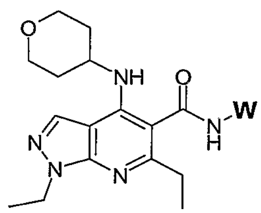
The following Examples 7-11 were prepared from Intermediate 21 and the appropriate amine WNH_2 using a similar procedure to that used for the preparation of Example 1:

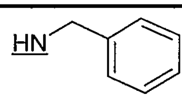
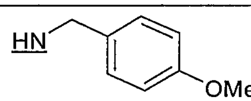
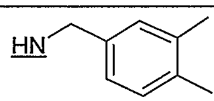
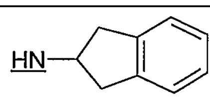
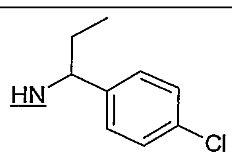


Example No.	NHW	Source of amine reagent WNH_2	MH^+ ion	T_{RET} (min)
7		Aldrich	422	2.71

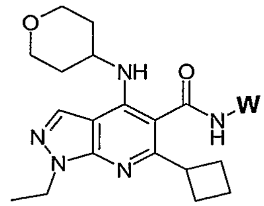
8		Aldrich	452	2.7
9		Matrix Scientific	470	3.09
10		Trans World Chemicals	450	2.99
11		Aldrich	448	2.86

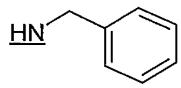
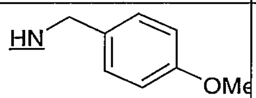
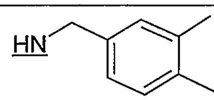
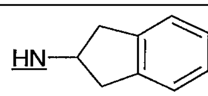
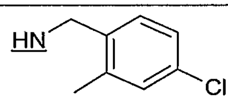
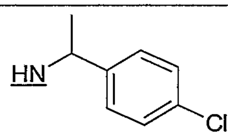
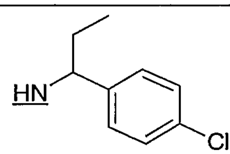
The following Examples 12-16 were prepared from Intermediate 22 and the appropriate amine WNH_2 using a similar procedure to that used for the preparation of Example 1:



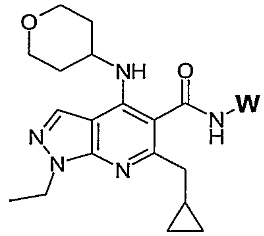
Example No.	NHW	Source of amine reagent WNH_2	MH^+ ion	T_{RET} (min)
12		Aldrich	408	2.43
13		Aldrich	438	2.44
14		Trans World Chemicals	436	2.75
15		Aldrich	434	2.6
16		J. Pharm. Pharmacol; 1997, 49 (1), 10-15	470	2.94

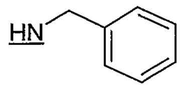
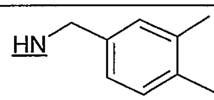
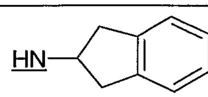
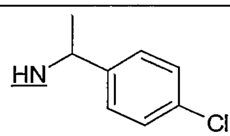
The following Examples 17-23 were prepared from Intermediate 23 and the appropriate amine WNH_2 using a similar procedure to that used for the preparation of Example 1:



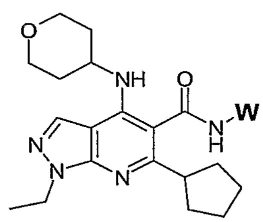
Example No.	**NHW**	**Source of amine reagent WNH_2**	**MH^+ ion**	**T_{RET} (min)**
17		Aldrich	434	3.17
18		Aldrich	464	3.14
19		Trans World Chemicals	462	3.42
20		Aldrich	460	3.34
21		Matrix Scientific	482	3.51
22		Bionet Research	482	3.45
23		J. Pharm. Pharmacol; 1997, 49 (1), 10-15	496	3.57

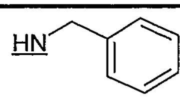
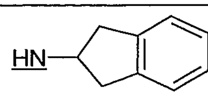
The following Examples 24-27 were prepared from Intermediate 24 and the appropriate amine WNH_2 using a similar procedure to that used for the preparation of Example 1:



Example No.	NHW	Source of amine reagent WNH_2	MH^+ ion	T_{RET} (min)
24		Aldrich	434	2.77
25		Trans World Chemicals	462	3.04
26		Aldrich	460	2.93
27		Bionet Research	482	3.09

The following Examples 28-29 were prepared from Intermediate 24 and the appropriate amine WNH_2 using a similar procedure to that used for the preparation of Example 1:



Example No.	NHW	Source of amine reagent WNH_2	MH^+ ion	T_{RET} (min)
28		Aldrich	448	3.33
29		Aldrich	474	3.45